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Preparation of novel 3*H*-trifluoromethyldiazirine-based photoactivatable potassium channel antagonists

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Abstract—The preparation of a series of photoactivatable precursors for use in photoaffinity labelling of potassium channels is described. 3*H*-Diazirine functionalities were incorporated into the previously described potassium channel antagonists **1**–**3**. The ability to perform enantioselective reductions and Wittig reactions in the presence of 3*H*-diazirines was central to this work.

1. Introduction

Ion channels are macromolecular protein complexes within cell membranes that mediate and regulate crucial electrical functions throughout the body. They are drug targets for a number of therapeutic agents aimed at treating a variety of disorders including hypertension, arrhythmias, seizures, pain, stroke, and diabetes. It has become evident that there are a multitude of channels, each having a highly evolved structure.

Much attention has been paid to the determination of the structure of voltage-activated (K_V) potassium channels as they are amongst the most functionally diverse of all the ion-channels, playing major roles in the control of cell excitability across a wide range of cell types.[1] Such structural information is important for the development of channel-specific antagonists (blockers) targeted to the brain, offering the potential to treat a number of currently untreatable or difficult to manage diseases such as multiple sclerosis.[2] Elegant structural studies have revealed much of the details concerning the structure and function of these channels.[3] They consist of tetrameric bundles of proteins, each of which is composed of six transmembrane helices (S1–S6).[4] The first four, and particularly S4, are responsible for detecting changes in membrane potential, S5, S6, and the connecting loop provide the ion-selectivity filter (Fig. 1).

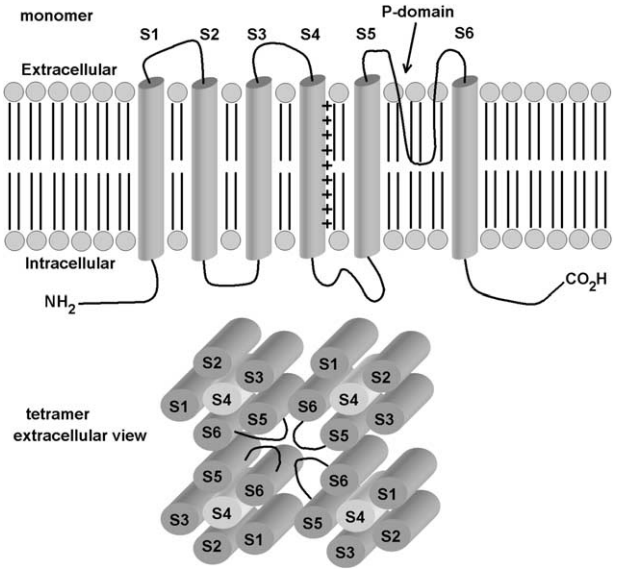

Figure 1.

Although many peptidic toxins show a high activity in the brain as K_V channel blockers, producing marked physiological responses,[5] to date there are few non-peptidic blockers targeted towards these channels. Among those described[6,7] is a series of open channel blockers of which **1**–**3** (Fig. 2) show a particularly interesting activity towards brain $K_V1.1$ channels, with IC_{50} values in the range 60–600 μM.

Photoaffinity labelling is a powerful tool for probing the structure of membrane proteins to elucidate otherwise

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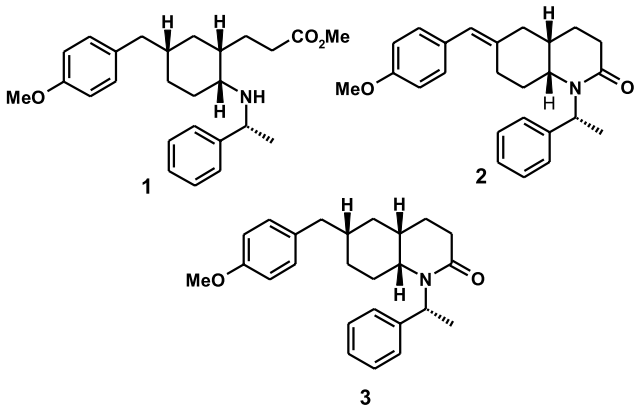


Figure 2.

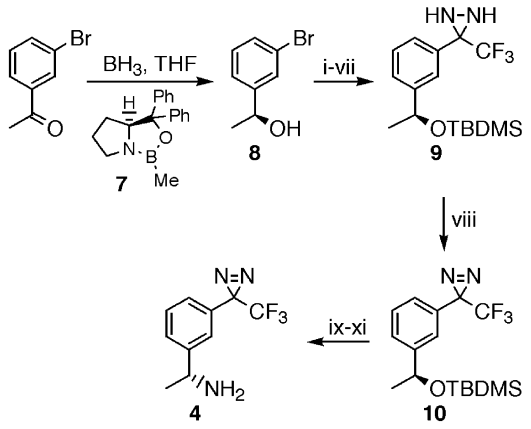
difficult to obtain structural information, such as the details of antagonist binding sites.[8] Various functional groups have been utilised as photocrosslinkable units for the study of biological systems, notably aryl ketones,[9] and azides.[8] Amongst these, the 3*H*-trifluoromethyl diazirines are particularly attractive due to their thermal stability and ability to release a highly reactive trifluoromethyl carbene upon photolysis at around 350 nm.[10–16] As the small molecule K_V channel blockers such as **1**–**3** (Fig. 2) offered the potential for investigating the possibility of these binding within the narrow part of the channel pore,[17] which is inaccessible to the larger peptidic blockers, it was highly desirable to prepare a number of photoactivatable derivatives of these molecules, incorporating 3*H*-trifluoromethyl diazirines to enable labelling studies to be performed on the brain $K_V1.1$ channel.

Despite their demonstrated potential as photolabile moieties, syntheses of non-peptidic 3*H*-trifluoromethyldiazirine-labelled substrates are few and there is presently only a limited knowledge of their behaviour under various chemical conditions. We therefore describe below the synthesis of a range of diazirine-based photoreactive antagonists, which illustrate the chemical robustness of this versatile photolabile moiety.

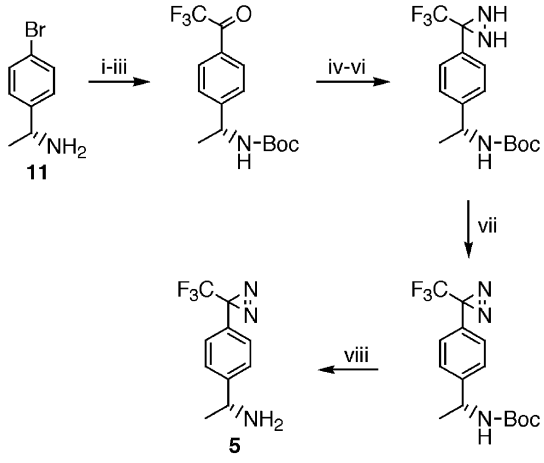
2. Results and discussion

In order to prepare photoactivatable analogues of **1**, our initial synthetic targets were chiral amines **4** and **5** (Schemes 1 and 2) to be used in the reductive amination of ketone **6** (Scheme 3). A high yielding preparation of chiral amine **4** was subsequently developed (Scheme 1). Thus, 3-bromoacetophenone was reduced to chiral alcohol **8** with borane in the presence of Corey's chiral oxazaborolidine **7**.[18] This was then protected as the *tert*-butyldimethylsilyl (TBDMS) ether by reaction of the sodium salt of the alcohol with TBDMS chloride in the presence of a catalytic amount of 15-crown-5 (Scheme 1).

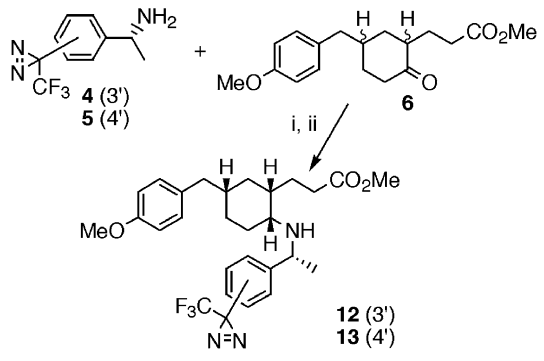
Diaziridine **9** was prepared from the silyl ether via a sequence involving formation of a trifluoromethyl ketone, oximation, and cyclisation of the *O*-tosylated oxime with ammonia.[19] During the course of this and other work, it became apparent to us that oxidation of trifluoromethyl



Scheme 1. Reagents and conditions: (i) NaH, 15-crown-5, DCM; (ii) TBDMS–Cl, 78%; (iii) *n*BuLi, THF, −78 °C; (iv) Et_2NCOCF_3, −78 °C, 91%; (v) $NH_2OH{\cdot}HCl$, pyridine, 99%; (vi) TsCl, DIEA, DMAP, DCM, 82%; (vii) NH_3, Et_2O, −78 °C, 79%; (viii) PCC, pyridine, DCM, 96%; (ix) TBAF, THF, H_2O, 2 h, 82%; (x) phthalimide, Ph_3P, DEAD, 50%; (xi) NH_2NH_2, MeOH, 83%.



Scheme 2. Reagents and conditions: (i) BOC–ON, DCM, 72%; (ii) *n*BuLi (2 equiv), THF; (iii) Et_2NCOCF_3, −78 °C, 82%; (iv) $NH_2OH{\cdot}HCl$, pyridine, Δ, 96%; (v) TsCl, DIEA, DMAP, DCM, 77%; (vi) NH_3, Et_2O, −78 °C, 95%; (vii) PCC, DCM, pyridine, 82%; (viii) HCOOH, Δ, 75%.



Scheme 3. Reagents and conditions: (i) AcOH (1.1 equiv), 3 Å sieves, DCE, 18 h; (ii) $NaBH(OAc)_3$, 4 h, 23% (**13**) 5% (**12**).

diaziridines such as **9** to yield the corresponding diazirine proceeds sluggishly using silver oxide, often requiring the addition of further quantities of freshly prepared reagent to the reaction. It was found, however, that this conversion could be readily achieved in excellent yield using PCC in DCM, being complete within 5 min. The addition of pyridine to the reaction mixture enabled diazirine **10** to be obtained without loss of the silyl protecting group; a problem described elsewhere[20] with PCC.

Following fluoride ion mediated removal of the silyl protecting group to give the alcohol; the corresponding protected amine was prepared, with inversion of stereochemistry,[21] using a Mitsunobu reaction with phthalimide. The phthaloyl group was subsequently removed using hydrazine in methanol. Chiral amine **5** was prepared in good yield from commercially available amine **11** as outlined in Scheme 2. Boc-protection of the amine and subsequent conversion to the diazirine proceeded smoothly. Final deprotection was achieved in good yield using formic acid to produce **5**.

Our initial strategy involved a nickel catalysed reductive amination of ketone **6**[6] with amines **4** and **5**. It was found, however, that the diazirine moiety was not stable under these conditions and reduction to a mixture of the corresponding trifluoromethyl hydrazone and 2,2,2-trifluoroethyl substituted system was observed. Sodium triacetoxyborohydride on the other hand, was found to be a suitably mild reducing agent, and by careful control of reaction conditions the *para*-substituted benzylamine **5** gave the desired stereoisomer **13** in modest yield but crucially, with the diazirine ring intact (Scheme 3).

It is interesting that, despite the rather modest yield, **13** was obtained as a single diastereoisomer, and no other isomeric amines were detected in the crude reaction mixtures (NMR), diazirine **13** being easily purified using column chromatography.

Stereochemical assignment was made by comparison of the NMR spectra of **13** to those of authentic samples of antagonist **1** and the stereoisomeric compounds **A–C** (Fig. 3).[22] In particular, comparison of the ^{13}C resonances revealed a close correspondence with those in the ^{13}C NMR spectrum of **1**, (Fig. 3).

A likely explanation for the observed stereocontrol is the differences in the rates of reduction of the various imine intermediates (Fig. 4). As the starting material **6** is a racemic mixture containing both cis- and trans-isomers, condensation with optically pure amine can yield up to four diastereoisomeric imines, reduction of which creates a fourth stereocentre yielding eight possible diastereoisomeric amines. The observed stereocontrol can be explained in terms of kinetic resolution of the imine corresponding to the desired product. It has already been demonstrated[23a–d] that bulky borohydride reducing agents favour equatorial attack from the least hindered face of 2-substituted exocyclic cyclohexylimine, producing an axial amine as the product (Fig. 4A). This mechanism operates due to the hindrance of axial attack resulting from the presence of the 3- and 5- axial hydrogens. As a

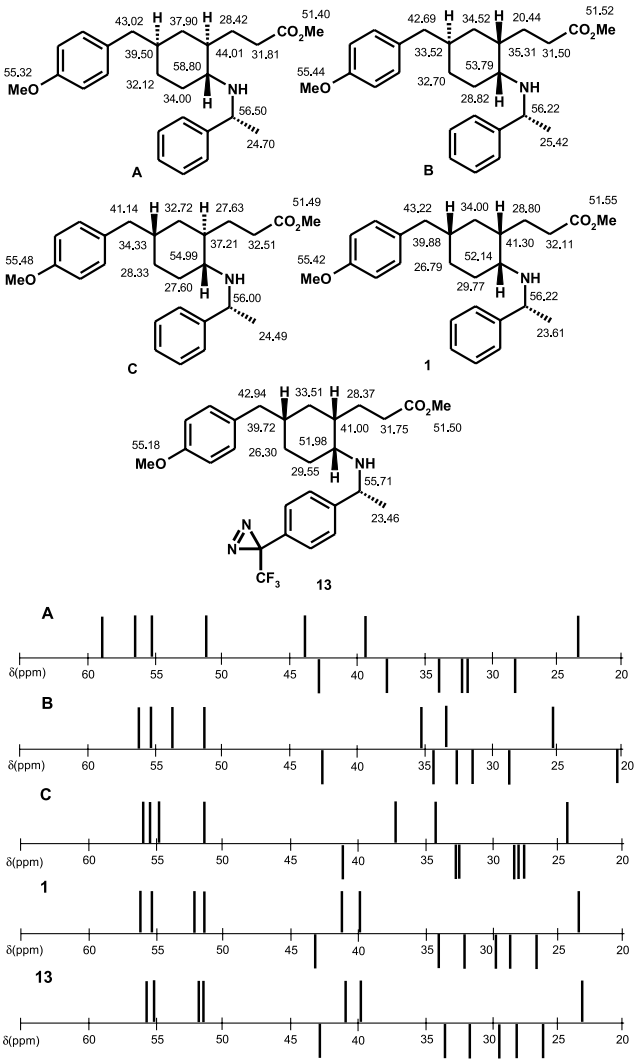


Figure 3. Schematic comparison of ^{13}C spectra (only high-field signals shown). Methine resonances identified using DEPT and are shown as inverted signals.

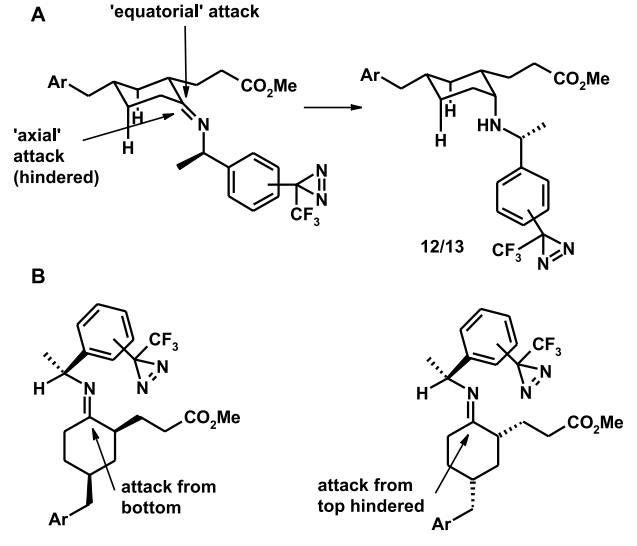


Figure 4.

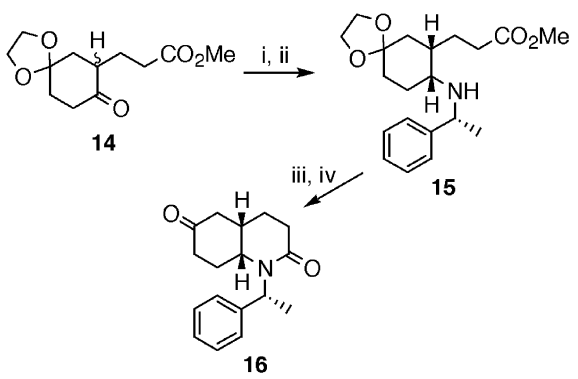
consequence, assuming that the 2-propionyl group is always equatorial, reduction by triacetoxyborohydride will always result in a cis relative sterochemical relationship with the amino group in the product. It is furthermore noteworthy that the 4-methoxybenzyl substituent is equatorial in the imines corresponding to the products **12** and **13**. The corresponding imine with the 4-substituent of opposite stereochemistry would have this substituent located axially, which would partially hinder equatorial attack by the borohydride, and also favour a high population of the chair conformation with the axially-located 2-substituent also blocking equatorial attack. The central issue to resolve is the selectivity observed between the two imines of opposing ring stereochemistry, which would both produce an all cis substitution pattern upon imine reduction (Fig. 4B). This is accounted for by the chirality of the methylbenzyl group. In both imines, this group is expected to be in the *E* conformation, with the methylbenzyl group directed away from the 2-propionyl substituent.

At the same time, however, the methylbenzyl substituent occupies conformations in which the aromatic ring and the methyl group partially obstruct attack on the imine carbon. In the case of the imine corresponding to **12** and **13**, the top face of the ring as seen in Figure 4B is obstructed. This is not significant, however, as equatorial attack occurs from the bottom face in this case.

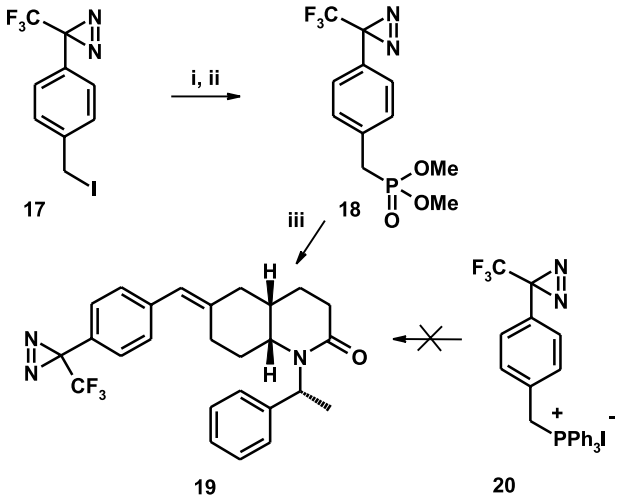
For the imine corresponding to the 'wrong' stereoisomer, the top face of the ring is still obstructed, and equatorial attack also occurs from this face. As a result, presumably, the rate of reduction of this imine is markedly decreased.

Although very low yielding, the *para*-subtituted benzylamine **4** similarly reacted with ketone **6** to give **12** as the sole product of reductive amination. In this case, stereochemistry was assigned via spectral comparison of the ^{1}H NMR spectrum to that of compound **13**.

In order to prepare a photoactivatable analogue of antagonist **2**, ketone **16** (Scheme 4) was prepared by the reductive amination of **14**[6] to give **15**, followed by lactamisation and acetal deprotection. Wittig–Horner reaction of this ketone with phosphonate **18**, prepared by reaction of benzyl iodide **17**[19] with trimethylphosphite, gave target olefin **19** in moderate yield (Scheme 5). Our initial



Scheme 4. Reagents and conditions: (i) *R*(+)-α-methylbenzylamine, TsOH, PhMe, Δ; (ii) Ni/H_2, 74%; (iii) AcOH, PhMe, Δ, 64%; (iv) AcOH, H_2O, Δ, 82%.



Scheme 5. Reagents and conditions: (i) $P(OMe)_3$ (10 equiv), PhMe; (ii) Δ, 18%; (iii) **16**, NaH, THF, 18 h, 27%.

intention to use phosphonium salt **20** for this reaction was unsuccessful as **20** proved to be too unreactive in the presence of ketone **16**, although it was observed to undergo reaction with simple aldehydes such as benzaldehyde (79% yield).

3. Conclusions

We have described the preparation of a number of reagents with important applications in photoaffinity labelling studies of voltage-activated potassium channels. This work has further explored the scope and limitations of reactions involving diazirine-containing substrates. In particular, the potential for use of the diazirine group in the preparation of photolabile substrates has been expanded by the preparation of diazirines of application in the derivatisation, via Wittig reaction, of aldehydes and ketones. Furthermore, a modest stability of the diazirine moiety in the presence of reducing agents has been demonstrated.

4. Experimental

4.1. General

Infrared spectra were recorded using a Perkin Elmer 1420 spectrometer. ^{1}H and ^{13}C NMR spectra were measured on General Electric QE 300 or Bruker AMX400 spectrometers using tetramethylsilane as the internal standard. Coupling constants (*J*) are quoted in Hertz. Low and high-resolution mass specta were recorded on an VG Autospec using either chemical ionisation (CI), electron impact (EI), or fast atom bombardment (FAB) ionisation techniques. All accurate mass measurements were performed using EI on signals of greater than 1% relative intensity. Optical rotations were determined at 30 °C using an Optical Activity AA1000 polarimeter with cells of path lengths 0.25 or 1 dm. Melting points were determined using a Reichert hot stage and are uncorrected. Microanalyses were performed by the University of Leeds Microanalytical service using an Elemental Analyser 1106. Flash column chromatography

was carried out using Merck Kieselgel 60 (230–400 mesh). Solvents were either obtained dry from commercial sources or dried prior to use using standard methods.

4.1.1. (*S*)-1-(3-Bromophenyl)ethyl alcohol (8). To a stirred solution of 3-bromoacetophenone (4.90 g, 24.6 mmol) and (*R*)-(+)-2-methyl-CBS-oxazaborolidine (0.74 g, 2.5 mmol) in THF (20 ml) under argon was added BH_3 (1.0 M in THF; 14.8 ml, 14.8 mmol) over 10 min. After stirring for a further 15 min the mixture was cooled to 0 °C and diluted with MeOH (60 ml). After 30 min HCl/Et_2O (60 ml) was added and the solution concentrated in vacuo. The resulting oily solid was washed with Et_2O (100 ml), the washings evaporated in vacuo and the oily residue chromatographed (hexane/Et_2O; 4:1) to give the title compound (2.63 g, 53%) as a colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$); δ 1.48 (3H, d, J=6.6 Hz, Me), 1.96 (1H, br, OH), 4.88 (1H, q, J=6.6 Hz, Me-C*H*(Ar)-OH), 7.19–7.39 (2H, m, Ar), 7.43 (1H, d, J=8.3 Hz, Ar), 7.55 (1H, d, J=9.6 Hz, Ar). ν/cm^{-1} (liquid film) 3370 (s), 2900 (s), 1600 (m), 1570 (s), 1430 (s), 1200 (s), 1070 (s), 905 (m), 785 (s), 700 (s). $[\alpha]_D^{30}$ −19 (*c* 0.9, $CHCl_3$). *m*/*z* (EI, %): 202 (20, M^+, ^{81}Br), 77 (100).

4.1.2. (*S*)-1-(3-Bromophenyl)ethyl alcohol-*O*-(*tert*-butyldimethylsilyl) ether. A solution of alcohol (**8**) (1.86 g, 9.3 mmol) in DCM (10 ml) was added dropwise to a stirred suspension of NaH (60% suspension in mineral oil; 0.64 g, 16.0 mmol) in DCM (10 ml) under argon at room temperature over a 10 min period. Following stirring for a further 10 min, a mixture of TBSMS–Cl (3.48 g, 23.1 mmol) and 15-crown-5 (0.2 g, 0.9 mmol) in DCM (10 ml) was added dropwise over 10 min. After stirring for a further 55 min, the reaction was quenched by the addition of ^{i}PrOH (50% aq, 45 ml) and the mixture diluted with DCM (60 ml). The organic layer was then washed with water (2× 100 ml), dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification using chromatography (hexane) gave the title compound (2.28 g, 78%) as a colourless liquid. ^{1}H NMR (200 MHz, $CDCl_3$); δ −0.02 (3H, s, Me-Si–), 0.93 (9H, s, ^{t}Bu), 1.40 (3H, d, J=6.4 Hz, *Me*-CH(Ar)-OSi), 4.84 (1H, q, J=6.2 Hz, Me-C*H*(Ar)-OSi), 7.15–7.29 (2H, m, Ar), 7.34–7.39 (1H, m, Ar), 7.49–7.50 (1H, m, Ar). ν/cm^{-1} (liquid film) 2960 (s), 1600 (m), 1570 (m), 1470 (s), 1260 (s), 1200 (s), 1120 (s), 1100 (s), 840 (s), 780 (s), 700 (s). $[\alpha]_D^{30}$ −23 (*c* 0.9, $CHCl_3$). *m*/*z* (CI (NH_3) %): 334 (1, $M^+ + NH_4$, ^{81}Br), 332 (0.8, $M^+ + NH_4$, ^{79}Br), 317 (1, $M^+ + H$, ^{81}Br), 315 (1, $M^+ + H$, ^{79}Br), 276 (11, ^{81}Br), 274 (14, ^{79}Br), 202 (47, ^{81}Br), 200 (50, ^{79}Br), 196 (27), 122 (100). $C_{14}H_{23}BrOSi$ requires: C, 53.3; H, 7.35. Found: C, 53.5; H, 7.37.

4.1.3. (*S*)-3-[1-(*tert*-Butyldimethylsiloxy)ethyl]-2,2,2-trifluoroacetophenone. To a stirred solution of (*S*)-1-(3-bromophenyl)ethyl alcohol-*O*-(*tert*-butyldimethylsilyl) ether (2.68 g, 8.5 mmol) at −78 °C under argon in THF (30 ml) was added ^{n}BuLi (1.6 M in hexane: 6.2 ml, 9.9 mmol) dropwise over 10 min. After stirring at −78 °C for a further 75 min, a solution of *N*,*N*-diethyltrifluoroacetamide (1.9 g, 11 mmol), in THF (6 ml) was added dropwise over 1 h. After stirring for a further 75 min at −78 °C, ammonium chloride (half satd aq solution; 30 ml) was added and the stirred mixture allowed to warm to room temperature. Diethyl ether (50 ml) was added and the organic layer separated and washed successively with ammonium chloride (satd aq; 2×50 ml) and water (3× 50 ml). Following drying ($MgSO_4$) of the combined organic solutions, filtration and removal of the solvents in vacuo, chromatography (hexane/EtOAc; 6:1) of the resulting yellow oil gave the title compound (2.57 g, 91%) as a colourless oil. ^{1}H NMR (200 MHz, $CDCl_3$); δ −0.02 (3H, s, *Me*-Si–), 0.09 (3H, s, *Me*-Si–), 0.93 (9H, s, ^{t}Bu), 1.44 (3H, d, J=6.4 Hz, *Me*-CH(Ar)-OSi), 4.96 (1H, q, J=6.2 Hz, Me-C*H*(Ar)-OSi), 7.51 (1H, t, J=7.8 Hz, Ar), 7.68–7.72 (1H, m, Ar), 7.94–7.98 (1H, m, Ar), 8.09 (1H, m, Ar). ν/cm^{-1} (liquid film) 2960 (s), 2920 (s), 1729 (s), 1605 (w), 1220 (s), 1200 (s), 1155 (s), 950 (m), 840 (s), 780 (m), 740 (m). $[\alpha]_D^{30}$ −23 (*c* 1.2, $CHCl_3$). *m*/*z* (EI, %): 332 (0.02, M^+), 276 (3), 263 (2), 225 (100), 131 (42), 103 (14), 75 (79). $C_{16}H_{23}F_3O_2Si$ requires: C, 57.03; H, 7.03. Found: C, 57.06; H, 7.09.

4.1.4. (*S*)-3-[1-(*tert*-Butyldimethylsiloxy)ethyl]-2,2,2-trifluoroacetophenone oxime. (*S*)-3-[1-(*tert*-butyldimethylsiloxy)ethyl]-2,2,2-trifluoroacetophenone (2.5 g, 7.56 mmol) and hydroxylamine hydrochloride (2.5 g, 7.56 mmol) were stirred together in a mixture of pyridine (27 ml) and EtOH (12 ml) at 80 °C for 4 h. Following removal of the solvents in vacuo, the residue was treated with Et_2O (70 ml) and washed with water (4×35 ml), dried ($MgSO_4$), filtered, and concentrated in vacuo. Chromatography (hexane/ether; 4:1) of the residue gave the title compound (2.61 g, 99%) as a colourless oil. ^{1}H NMR (200 MHz, $CDCl_3$); δ −0.02 (3H, s, *Me*-Si–), 0.05 (3H, s, *Me*-Si–), 0.90 (9H, s, ^{t}Bu), 1.41 and 1.44 (3H, d, J=6.4 Hz, *Me*-CH(Ar)-OSi, E/Z oxime), 4.90 (1H, q, J=6.4 Hz, Me-C*H*(Ar)-OSi), 7.35–7.48 (4H, m, Ar), 8.42 (1H, br, –OH). ν/cm^{-1} (liquid film) 3300 (m), 2970 (s), 2920 (s), 1260 (m), 1230 (m), 1170 (s), 1100 (m), 835 (s), 780 (m). $[\alpha]_D^{30}$ −22 (*c* 0.6, $CHCl_3$). *m*/*z* (CI (NH_3), trimethylsilyl derivative, %): 420 (52, $M^+ + H$), 352 (3), 332 (100), 305 (15), 288 (12). $C_{16}H_{24}F_3NO_2Si$ requires: C, 55.3; H, 6.96; N, 4.0. Found: C, 57.06; H, 6.65; N, 3.5.

4.1.5. (*S*)-3-[1-(*tert*-Butyldimethylsiloxy)ethyl]-2,2,2-trifluoroacetophenone-*O*-(4-toluenesulphonyl)oxime. 4-Toluenesulphonyl chloride (1.4 g, 7.4 mmol) was added portion-wise to a stirred solution of (*S*)-3-[1-(*tert*-butyldimethylsiloxy)ethyl]-2,2,2-trifluoro acetophenone oxime (2.58 g, 7.4 mmol), DIEA (1.4 ml, 8.3 mmol) and DMAP (70 mg, 0.56 mmol) in DCM (12.5 ml) at 0 °C. The stirred mixture was allowed to warm to room temperature over 40 min and was washed with water (3×15 ml) and dried ($MgSO_4$). Following filtration and concentration in vacuo, chromatography (DCM/petrol; 3:4) gave the title compound (3.07 g, 82%) as a colourless oil. ^{1}H NMR (200 MHz, $CDCl_3$); δ −0.03 and −0.04 (3H, s, *Me*-Si–, E/Z oxime), 0.06 (3H, s, *Me*-Si–), 0.89 (9H, s, ^{t}Bu), 1.38 and 1.40 (3H, d, J=6.4 Hz, *Me*-CH(Ar)-OSi, E/Z oxime), 2.46 and 2.48 (3H, s, *Me*-PhSO_2–, E/Z oxime), 4.88 (1H, m, Me-C*H*(Ar-OSi), 7.24–7.50 (6H, m, Ar), 7.86–7.93 (2H, m, Ar). ν/cm^{-1} (liquid film) 2970 (m), 2920 (m), 1600 (w), 1390 (s), 1200 (s), 1180 (s), 1095 (m), 830 (s), 780 (s). $[\alpha]_D^{30}$ −15 (*c* 0.6, $CHCl_3$). *m*/*z* (CI (NH_3), %): 519 (1, $M^+ + NH_4$), 351 (11), 332 (100), 219 (5), 204 (10).

4.1.6. (*S*)-3-Trifluoromethyl-3-{3-[1-(*tert*-butyl dimethylsiloxy)ethyl]phenyl}diaziridine (9). To a stirred solution of (*S*)-3-[1-(*tert*-butyldimethylsiloxy)ethyl]-2,2,2-trifluoroacetophenone -*O*-(4-toluenesulphonyl) oxime (2.95 g,

5.9 mmol), in ether (12 ml) at −78 °C in a 3-neck flask fitted with a CO_2/acetone condenser and potassium carbonate guard tube, was added ammonia (36 ml) by direct distillation from sodium over an 8 h period and this solution then stirred at −78 °C for 2 h. The ammonia was then allowed to evaporate via allowing the solution to warm to room temperature over a 7 h period. The ethereal solution was filtered and the solvent removed in vacuo to give the title compound (1.61 g, 79%) as a colourless oil. ^{1}H NMR (200 MHz, $CDCl_3$); δ −0.04 (3H, s, *Me*-Si–), 0.07 (3H, s, *Me*-Si–), 0.88 (9H, s, ^{t}Bu), 2.22 (1H, d, J=8.7 Hz, –N*H*–NH–), 2.80 (1H, d, J=8.7 Hz, –NH–N*H*–), 1.42 (3H, d, J=6.4 Hz, *Me*-CH(Ar)-OSi), 4.86 (1H, q, J=6.5 Hz, Me-C*H*(Ar)-OSi), 7.29–7.62 (4H, m, Ar). ν/cm^{-1} (liquid film) 3260 (m), 2920 (s), 1720 (w), 1460 (m), 1250 (m), 1170 (s), 1140 (s), 970 (m), 830 (s), 770 (m). $[\alpha]_D^{30}$ −24 (*c* 1.0, $CHCl_3$). *m*/*z* (EI, %): 346 (0.1, M^+), 331 (0.5), 274 (9), 224 (22), 208 (13), 130 (44), 75 (100). $C_{16}H_{25}F_3N_2OSi$ requires: C, 55.5; H, 7.3; N, 8.1. Found: C, 55.4; H, 7.0; N, 7.8.

4.1.7. (*S*)-1-[3-(3-Trifluoromethyl-3*H*-diazirin-3-yl)-phenyl]ethyl alcohol-*O*-*tert*-butyldimethylsilyl ether (10). To a stirred solution of (*S*)-3-trifluoromethyl-3-{3-[1-(*tert*-butyldimethylsiloxy)ethyl]phenyl}diaziridine (0.99 g, 2.8 mmol) and pyridine (2.5 ml) in DCM (25 ml) was added PCC (0.92 g, 2.8 mmol) over 10 min. Following dilution with ether (25 ml), the mixture was filtered through a pad of silica and concentrated in vacuo. Chromatography (hexane/ether; 4:1) gave the title compound (0.94 g, 96%) as a pale yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$); δ −0.04 (3H, s, *Me*-Si–), 0.05 (3H, s, *Me*-Si–), 0.90 (9H, s, ^{t}Bu), 1.38 (3H, d, J=6.3 Hz, *Me*-CH(Ar)-OSi), 4.86 (1H, q, J=6.3 Hz, Me-C*H*(Ar)-OSi), 7.02–7.04 (1H, m, Ar), 7.20 (1H, br s, Ar), 7.28–7.35 (2H, m, Ar). ν/cm^{-1} (liquid film) 2960 (s), 2930 (s), 1610 (m), 1250 (s) 1200 (s), 1150 (s), 950 (m), 830 (s), 780 (m), 700 (m). $[\alpha]_D^{30}$ −24 (*c* 1.2, $CHCl_3$). *m*/*z* (EI, %): 344 (0.1, M^+), 259 (3), 149 (20), 81 (61), 69 (100). $C_{16}H_{23}F_3N_2OSi$ requires: C, 55.79; H, 6.73; N, 8.13. Found: C, 55.64; H, 7.20; N, 8.05.

4.1.8. (*S*)-1-[3-(3-Trifluoromethyl-3*H*-diazirin-3-yl)-phenyl]ethyl alcohol. (*S*)-1-[3-(3-trifluoromethyl-3*H*-diazirin-3-yl)phenyl]ethyl alcohol-*O*-*tert*-butyldimethylsilyl ether (0.29 g, 0.83 mmol) was treated with a solution of TBAF (1.6 M in THF; 6.8 ml, 10.9 mmol) containing 5% water for 2 h at 20 °C. Following dilution with ether (20 ml), the mixture was washed with water (2×20 ml) and dried ($MgSO_4$). Following filtration and evaporation in vacuo, chromatography (ether) gave the title compound (0.16 g, 82%) as a yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$); δ 1.48 (3H, d, J=6.6 Hz, *Me*-CH(Ar)-OH), 1.85 (1H, br, –OH), 4.90 (1H, q, J=6.6 Hz, Me-C*H*(Ar)-OH), 7.13–7.16 (2H, m, Ar), 7.34–7.45 (2H, m, Ar). ν/cm^{-1} (liquid film) 3350 (s), 2980 (m), 2910 (m), 1610 (m), 1240 (s), 1200 (s), 1160 (s), 900 (m), 800 (m), 700 (m). $[\alpha]_D^{30}$ −25 (*c* 0.9, $CHCl_3$). *m*/*z* (EI, %): 230 (0.5, M^+), 206 (6), 187 (27), 159 (32), 137 (43), 109 (57), 91 (100). $C_{10}H_9F_3N_2O$ requires: C, 52.2; H, 3.9; N, 12.2. Found: C, 52.4; H, 4.0; N, 11.9.

4.1.9. (*R*)-*N*-{1-[3-(3-Trifluoromethyl-3*H*-diazirin-3-yl)-phenyl]ethyl}phthalimide. To a stirred solution of (*S*)-1-[3-(3-trifluoromethyl-3*H*-diazirin-3-yl)phenyl]ethyl alcohol (0.26 g, 1.1 mmol), triphenylphosphine (0.36 g, 1.4 mmol), and phthalimide (0.22 g, 1.5 mmol) in THF (25 ml) under argon, was added DEAD (0.22 ml, 1.4 mmol) dropwise over 2 min. After stirring the resulting pale yellow solution at room temperature for 4 days, the solvent was removed in vacuo and the residue chromatographed (pentane/ether; 4:1) to give the title compound (0.21 g, 50%) as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$); δ 1.90 (3H, d, J=7.2 Hz, *Me*-CH(Ar)-N–), 5.54 (1H, q, J=7.4 Hz, Me-C*H*(Ar)-N), 7.17 (1H, d, J=6.2 Hz, Ar), 7.30–7.39 (2H, m, Ar), 7.57–7.59 (1H, m, Ar), 7.69–7.72 (2H, m, Ar), 7.79–7.84 (2H, m, Ar). ν/cm^{-1} (liquid film) 3080 (m), 2940 (m), 1710 (s), 1610 (m), 1390 (s), 1245 (s), 1200 (s), 1145 (s), 900 (m), 875 (m), 795 (m), 725 (s), 700 (s). $[\alpha]_D^{30}$ −17 (*c* 0.3, $CHCl_3$). *m*/*z* (EI, %): 359 (0.7, M^+), 331 (36), 316 (16), 262 (67), 220 (26), 205 (85), 183 (58), 43 (100). $C_{18}H_{12}F_3N_3O_2$ requires: C, 60.17; H, 3.37; N, 11.69. Found: C, 60.31; H, 3.66; N, 11.66.

4.1.10. (*R*)-1-[3-(3-Trifluoromethyl-3*H*-diazirin-3-yl)-phenyl]ethylamine (4). A solution of (*R*)-*N*-{1-[3-(3-trifluoromethyl-3*H*-diazirin-3-yl)phenyl]ethyl} phthalimide (0.1 g, 0.28 mmol) in MeOH (5 ml) was treated with hydrazine (2.0 M solution in MeOH; 5 ml, 10 mmol) and this mixture stirred at room temperature for 17 h before the solvent was removed in vacuo. The residue was treated with chloroform and filtered before being washed with water (2×20 ml), dried ($MgSO_4$), filtered, and concentrated in vacuo to give the title compound (0.05 g, 83%) as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$); δ 1.36 (3H, d, J=6.6 Hz, *Me*-CH(Ar)–NH_2), 4.13 (1H, q, J=6.3 Hz, Me-C*H*(Ar)–NH_2), 7.12–7.16 (1H, m, Ar), 7.31–7.43 (3H, m, Ar). ν/cm^{-1} (liquid film) 3480 (w), 3225 (w), 2920 (s), 2845 (s), 1545 (w), 1465 (m), 1440 (m), 1165 (s), 1125 (s), 790 (m), 700 (m). $[\alpha]_D^{30}$ −8 (*c* 0.05, $CHCl_3$). *m*/*z* (EI, %): 229 (0.8, M^+), 216 (8), 201 (33), 183 (100), 167 (29), 149 (78), 108 (28). $C_{10}H_{10}F_3N_3$ requires: 229.082682. Found: 229.083022.

4.1.11. (*R*)-*N*-(*tert*-Butoxycarbonyl)-1-(4-bromophenyl) ethylamine. To a solution of (*R*)-1-(4-bromophenyl) ethylamine (**11**) (3.07 g, 15.3 mmol) and triethylamine (3 ml, 21.5 mmol) in DCM (15 ml) was added 2-(*tert*-butoxycarbonyloxyimino)-2-phenylacetonitrile (4.06 g, 16.5 mmol) at room temperature. The mixture was stirred for 70 min and was then diluted with DCM and the organic extracts dried ($MgSO_4$), filtered, and the solvents removed in vacuo. Recrystallisation from EtOAc/hexane gave the title compound (3.32 g, 72%) as a colourless solid, mp 131–135 °C. ^{1}H NMR (200 MHz, $CDCl_3$); δ 1.40–1.44 (12H, br m, ^{t}Bu and Me, E/Z Boc-NH), 4.65–4.80 (2H, br m, Me-C*H*(Ar)-NH-Boc and -N*H*-Boc, E/Z Boc-NH), 7.17 (2H, d, J=8.4 Hz, Ar), 7.43–7.47 (2H, m, Ar, E/Z Boc-NH). ν/cm^{-1} (liquid film) 3380 (s), 1680 (s), 1520 (s), 1250 (s), 1170 (s), 1060 (s), 830 (s). $[\alpha]_D$ −48 (*c* 0.9, $CHCl_3$). *m*/*z* (CI, (NH_3), %): 319 (2, $M^+ + NH_4$, ^{81}Br), 317 (2, $M^+ + NH_4$, ^{79}Br), 263 (38, ^{81}Br), 261 (37, ^{79}Br), 219 (21, ^{82}Br), 217 (23, ^{79}Br), 202 (98, ^{81}Br), 200 (100, ^{79}Br). $C_{13}H_{18}BrNO_2$ requires: C, 52.0; H, 6.0; N, 4.7. Found: C, 51.9; H, 6.0; N, 4.6.

4.1.12. (*R*)-*N*-(*tert*-Butoxycarbonyl)-4-[(1-amino)ethyl]-2,2,2-trifluoroacetophenone. The title compound was prepared from (*R*)-*N*-(*tert*-butoxycarbonyl)-1-(4-bromophenyl)ethylamine (2.0 g, 6.7 mmol) using the method

described above (Section 4.1.3) for the preparation of (*S*)-3-[1-(*tert*-butyldimethylsiloxy)ethyl]-2,2,2-trifluoroacetophenone. Purification using chromatography (hexane/ether; 4:1) gave the title compound (1.69 g, 84%) as a pale yellow solid, mp 75–76 °C. ^{1}H NMR (200 MHz, $CDCl_3$); δ 1.40–1.47 (12H, br m, ^{t}Bu and Me, E/Z Boc-NH), 4.72–5.00 (2H, br m, Me-C*H*(Ar)-NHBoc and –N*H*-Boc, E/Z Boc-NH), 7.48 (2H, d, J=8.2 Hz, Ar), 8.05 (2H, d, J=8.0 Hz, Ar). ν/cm^{-1} (nujol mull) 3380 (s), 1730 (s), 1680 (s), 1530 (s), 1220 (s), 1180 (s), 1130 (s), 1060 (s), 950 (s), 870 (m), 770 (m), 730 (m). $[\alpha]_D^{30}$ −44 (*c* 0.9, $CHCl_3$). *m*/*z* (EI, %): 302 (0.2, M^+), 262 (10), 246 (12), 202 (23), 201 (14), 57 (100). $C_{15}H_{18}F_3NO_3$ requires: C, 56.8; H, 5.7; N, 4.4. Found: C, 56.8; H, 6.0; N, 4.7.

4.1.13. (*R*)-*N*-(*tert*-Butoxycarbonyl)-4-[(1-amino)ethyl]-2,2,2-trifluoroacetophenone oxime. The title compound was prepared from (*R*)-*N*-(*tert*-butoxycarbonyl)-4-[(1-amino)ethyl]-2,2,2-trifluoroacetophenone (0.75 g, 2.4 mmol) using the method described above for the preparation of (*S*)-3-[1-(*tert*-butyldimethylsiloxy)ethyl]-2,2,2-trifluoroacetophenone oxime (Section 4.1.4) but replacing ether for ethyl acetate in the work-up. Purification using chromatography ($CHCl_3$/MeOH; 20:1) gave the title compound (0.76 g, 96%) as a pale yellow solid, mp 86–89 °C. ^{1}H NMR (200 MHz, $CDCl_3$); δ 1.41–1.43 (12H, br m, ^{t}Bu and Me, E/Z Boc-NH), 4.65–4.95 (2H, br m, Me-C*H*(Ar)-NHBoc and –N*H*-Boc, E/Z Boc-NH), 7.26–7.47 (4H, m, Ar), 8.91 and 9.27 (1H, br, OH, E/Z oxime). ν/cm^{-1} (nujol mull) 3390 (s), 3280 (br m), 1680 (s), 1520 (s), 1210 (s), 1180 (s), 1170 (s), 1060 (s), 950 (s), 830 (m), 730 (m). $[\alpha]_D^{30}$ −49 (*c* 0.7, $CHCl_3$). *m*/*z* (CI (NH_3), %): 334 (0.2, M^++2H), 278 (13), 243 (15), 219 (52), 217 (100), 202 (56), 200 (56), 122 (96). $C_{15}H_{19}F_3N_2O_3$ requires: C, 54.2; H, 5.8; N, 8.4. Found: C, 54.4; H, 5.8; N, 8.4.

4.1.14. (*R*)-*N*-(*tert*-Butoxycarbonyl)-4-[(1-amino)ethyl]-2,2,2-trifluoroacetophenone-*O*-(4-toluenesulphonyl) oxime. The title compound was prepared from (*R*)-*N*-(*tert*-butoxycarbonyl)-4-[(1-amino)ethyl]-2,2,2-trifluoroacetophenone oxime (0.71 g, 2.13 mmol) using the method described above for (*S*)-3-[1-(*tert*-butyldimethylsiloxy) ethyl]-2,2,2-trifluoroacetophenone-*O*-(4-toluenesulphonyl) oxime (Section 4.1.5). Purification using chromatography (hexane/ether; 3:2) gave the title compound (0.79 g, 77%) as a colourless solid, mp 146–149 °C. ^{1}H NMR (200 MHz, $CDCl_3$); δ 1.41–1.44 (12H, br m, ^{t}Bu and Me, E/Z Boc-NH), 2.47 and 2.48 (3H, s, *Me*$PhSO_2$, E/Z oxime), 4.71–4.86 (2H, br m, Me-C*H*(Ar)-NHBoc and –N*H*-Boc, E/Z Boc-NH), 7.31–7.43 (6H, m, Ar), 7.87 and 7.92 (2H, m, Ar). ν/cm^{-1} (nujol mull) 3380 (s), 1680 (s), 1530 (s), 1395 (s), 1190 (s), 1180 (s), 1060 (m), 880 (m), 820 (m), 730 (m). $[\alpha]_D^{30}$ −31 (*c* 1.0, $CHCl_3$) *m*/*z* (CI (NH_3), %): 504 (1.5, $M^+ + NH_4$), 448 (2), 317 (41), 261 (66), 243 (100), 217 (85), 204 (48), 122 (52). $C_{22}H_{25}F_3N_2O_5S$ requires: C, 54.3; H, 5.2; N, 5.8. Found: C, 54.6; H, 5.5; N, 5.7.

4.1.15. (*R*)-4-{*N*-(*tert*-Butoxycarbonyl)-(1-amino)ethyl}-3-trifluoromethyl diaziridine. The title compound was prepared from (*R*)-*N*-(*tert*-butoxycarbonyl)-4-[(1-amino) ethyl]-2,2,2 trifluoro acetophenone-*O*-(4-toluenesulphonyl) oxime (0.50 g, 1.03 mmol) using the method described above for (*S*)-3-trifluoromethyl-3-{3-[1-(*tert*-butyldimethylsiloxy)ethyl]phenyl}diaziridine (**9**) (Section 4.1.6). Purification using chromatography (hexane/ether; 3:2) gave the title compound (0.32 g, 95%) as a colourless solid, mp 117–118 °C. ^{1}H NMR (200 MHz, $CDCl_3$); δ 1.40–1.45 (12H, br m, ^{t}Bu and Me, E/Z Boc-NH), 2.20 (1H, d, J= 8.8 Hz, N*H*-NH), 2.78 (1H, d, J=8.8 Hz, NH-N*H*), 4.70–4.88 (2H, br m, Me-C*H*(Ar)-NHBoc and –N*H*-Boc, E/Z Boc-NH), 7.33–7.37 (2H, m, Ar), 7.58 (2H, d, J=8.2 Hz, Ar). ν/cm^{-1} (nujol mull) 3380 (s), 3270 (m), 1680 (s), 1520 (s), 1250 (s), 1220 (s), 1170 (s), 1140 (s), 1070 (m), 950 (m), 830 (s), 705 (m). $[\alpha]_D^{30}$ −40 (*c* 0.7, $CHCl_3$). *m*/*z* (EI, %): 331 (0.3, M^+), 316 (3), 274 (76), 215 (80), 187 (66), 145 (44), 57 (100). $C_{15}H_{20}F_3N_3O_2$ requires: C, 54.4; H, 6.1; N, 12.7. Found: C, 54.8; H, 6.2; N, 12.6.

4.1.16. (*R*)-*N*-(*tert*-Butoxycarbonyl)-1-[4-(3-trifluoromethyl-3*H*-diazirin-3-yl)phenyl]ethylamine. The title compound was prepared from (*R*)-4-{*N*-(*tert*-butoxycarbonyl)-(1-amino)ethyl}-3-trifluoro methyl diaziridine 0.30 g, 0.9 mmol) using the method described above for (*S*)-1-[3-(3-trifluoromethyl-3*H*-diazirin-3-yl)phenyl]ethyl alcohol-*O*-*tert*-butyldimethyl silyl ether (Section 4.1.7). The crude yellow solid was recrystallised from EtOAc/pentane to give the title compound (0.24 g, 82%) as a colourless solid, mp 163–167 °C (dec). ^{1}H NMR (200 MHz, $CDCl_3$); δ 1.39–1.43 (12H, br m, ^{t}Bu and Me, E/Z Boc-NH), 4.67–4.82 (2H, br m, Me-C*H*(Ar)-NHBoc and –N*H*-Boc, E/Z Boc-NH), 7.16 (2H, d, J=8.0 Hz, Ar), 7.33 (2H, d, J=8.1 Hz, Ar). ν/cm^{-1} (nujol mull) 3390 (s), 1680 (s), 1520 (s), 1240 (m), 1200 (s), 1150 (s), 1070 (m), 940 (m). $[\alpha]_D^{30}$ −38 (*c* 0.16, $CHCl_3$). *m*/*z* (EI, %): 329 (0.4, M^+), 314 (0.3), 301 (4), 272 (7), 245 (74), 200 (62), 57 (100). $C_{15}H_{28}F_3N_3O_2$ requires: C, 54.7; H, 5.5; N, 12.8. Found: C, 54.9; H, 5.5; N, 12.7.

4.1.17. (*R*)-1-[4-(3-Trifluoromethyl-3*H*-diazirin-3-yl)-phenyl]ethylamine (5). (*R*)-*N*-(*tert*-butoxycarbonyl)-1-[4-(3-trifluoromethyl-3*H*-diazirin-3-yl)phenyl]ethylamine (0.1 g, 0.3 mmol) was treated with formic acid (5 ml) and the mixture stirred for 2.5 h at room temperature before being concentrated in vacuo and diluted with ether (20 ml). The ethereal solution was treated with sodium bicarbonate solution (1 M aq) until effervescence ceased and the aqueous layer adjusted to pH 14 with KOH solution (10 M aq). After separation, the organic layer was washed with NaCl solution (satd aq; 20 ml), dried (K_2CO_3), filtered and concentrated in vacuo to give a yellow oil. Purification using column chromatography ($CHCl_3$/MeOH/20: 1) gave the title compound (0.052 g, 75%) as a yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$); δ 1.36 (3H, d, J=6.6 Hz, Me), 4.15 (1H, q, J=6.6 Hz, Me-C*H*(Ar)-NH_2), 7.16 (2H, d, J= 8.0 Hz, Ar), 7.39 (2H, d, J=8.0 Hz, Ar). ν/cm^{-1} (liquid film); 3370 (m), 3300 (m), 2980 (m), 1620 (m), 1345 (s), 1230 (s), 1180 (s), 1160 (s), 930 (s), 820 (s). $[\alpha]_D^{30}$ −20 (*c* 0.3, $CHCl_3$). *m*/*z* (EI, %): 229 (6, M^+), 202 (42), 186 (97), 184 (100), 162 (21). $C_{10}H_{10}F_3N_3$ requires: 229.082682. Found: 229.081616.

4.1.18. Methyl(1′*R*,1*S*,2*R*,5*S*)-5-[(4-methoxyphenyl) methyl]-2-{1′-[4-(3-trifluoromethyl-3*H*-diazirin-3-yl) phenyl]ethylamino}cyclohexanepropionate (13). A mixture of (±)-3-[2-oxo-5-(4-methoxybenzyl)cyclohexyl]-propionic acid methyl ester (**6**) (0.134 g, 0.44 mmol), (*R*)-1-[4-(3-trifluoromethyl-3*H*-diazirin-3-yl)phenyl]ethylamine

(**5**) (0.100 g, 0.44 mmol), AcOH (25 μl, 0.44 mmol) and 3 Å molecular sieves (powdered; 3 g) in DCE (4 ml) was stirred under argon at room temperature for 17 h before the addition of $NaBH(OAc)_3$ (0.120 g, 0.57 mmol). After stirring for a further 5.5 h, the mixture was filtered through a porosity three sinter, and the sieves washed with $CHCl_3$ (2×10 ml). The combined organic extracts were then washed successively with NaOH solution (1 M aq; 25 ml) and H_2O (2×25 ml) before being dried (K_2CO_3), filtered and concentrated in vacuo to give a green oil. Purification using flash column chromatography (pentane/Et_2O; 4:1) gave the title compound (0.051 g, 23%) as a yellow oil. ^1H NMR (400 MHz, $CDCl_3$); δ 0.89–1.08 (4H, m), 1.24–1.80 (10H, m), 2.26–2.45 (4H, m), 2.79–2.80 (1H, m), 3.66 (3H, s, $-CO_2Me$), 3.73–3.79 (4H, m, *Me*OPh– and Me-C*H*(Ar)-NH–), 6.80 (2H, d, $J=8.5$ Hz, Ar), 7.01 (2H, d, $J=8.1$ Hz, Ar), 7.13 and 7.24 (2H, d, $J=8.3$ Hz, Ar), 7.39 and 7.42 (2H, d, $J=8.3$ Hz, Ar). ^{13}C NMR (100 MHz, $CDCl_3$); δ 23.46, 26.30, 28.37, 29.55, 31.75, 33.51, 39.72, 41.00, 42.94, 51.50, 51.98, 55.18, 55.71, 113.46, 122.02 (q, $J=$ 67.8 Hz, $-CF_3$), 126.38, 127.11, 128.40, 129.87, 131.28, 132.91, 149.32, 157.62, 174.40. ν/cm^{-1} (liquid film) 3350 (w), 2920 (s), 1730 (s), 1610 (s), 1505 (s), 1445 (s), 1240 (s), 1180 (s), 1040 (m), 940 (m), 825 (m). $[\alpha]_D^{30}$ +7 (*c* 0.1, $CHCl_3$). *m*/*z* (EI, %): 517 (4, M^+), 489 (20), 474 (13), 240 (20), 200 (22), 185 (25), 149 (33), 121 (100). $C_{28}H_{34}F_3N_3O_3$ requires: 517.255227. Found: 517.254865.

4.1.19. Methyl(1′*R*,1*S*,2*R*,5*S*)-5-[(4-methoxyphenyl) methyl]-2-{1′-[3-(3-trifluoromethyl-3*H*-diazirin-3-yl) phenyl]ethylamino}cyclohexanepropionate (12). The title compound was prepared from (*R*)-1-[3-(3-trifluoromethyl-3*H*-diazirin-3-yl)phenyl]ethylamine (**4**) (0.040 g, 0.175 mmol) and (±)-3-[2-oxo-5-(4-methoxybenzyl)cyclohexyl]propionic acid methyl ester (**6**) (0.054 g, 0.177 mmol) using the method described above for the preparation of amine (**13**) (Section 4.1.8). Purification of the crude product using flash column chromatography (pentane/Et_2O; 4:1) gave the title compound (0.023 g, 5%) as a pale yellow oil. ^1H NMR (300 MHz, $CDCl_3$); δ 0.90–1.11 (4H, m), 1.22–1.70 (10H, m), 2.30–2.49 (4H, m), 2.79–2.80 (1H, m), 3.63 (3H, s, $-CO_2Me$), 3.72–3.80 (4H, m, *Me*OPh– and Me-C*H*(Ar)-NH–), 6.81 (2H, d, $J=8.2$ Hz, Ar), 7.03 (2H, d, $J=$ 8.5 Hz, Ar), 7.06–7.20 (1H, m, Ar), 7.31 and 7.40 (3H, m, Ar). ν/cm^{-1} (liquid film) 3350 (w), 2910 (s), 2850 (m), 1740 (s), 1615 (w), 1515 (s), 1250 (s), 1160 (s). $[\alpha]_D^{30}$ −9 (*c* 0.1, $CHCl_3$). *m*/*z* (EI, %): 517 (6, M^+), 489 (5), 304 (5), 268 (21), 240 (12), 185 (24), 149 (34), 121 (100). $C_{28}H_{33}F_3N_3O_3$ requires: 517.255227. Found: 517.254469.

4.1.20. Methyl(1′*R*,1*S*,2*R*)-5-[spiro-(2,5-oxa)cyclopentyl]-2-[1′-(phenylethyl)amino]cyclohexanepropionate (15). A mixture of 4-toluenesulphonic acid (0.05 g, 0.3 mmol), (±) methyl (2,5-oxo)-5-[spiro-(2,5-oxa)cyclopentyl]cyclohexane propionate (5.0 g, 20.6 mmol) and *R*(+)-α-methylbenzylamine (2.62 g, 23.3 mmol) in toluene (60 ml) was heated at reflux with a Dean-Stark water separator for 23 h, before the solvent was removed in vacuo and the residue dissolved in ethanol. To this was added Raney nickel (prepared from 1 g of a slurry in water) and the mixture stirred under an atmosphere of hydrogen for 6 days. Following filtration of the mixture through a pad of silica, the residue was concentrated in vacuo and purified using chromatography to give the title compound (5.23 g, 74%) as a colourless oil. ^1H NMR (300 MHz, $CDCl_3$); δ 1.31 (3H, d, $J=6.6$ Hz, *Me*-CH(Ar)-NH–), 1.42–1.83 (7H, m), 1.91–2.12 (1H, m), 2.35–2.41 (3H, m), 2.60–2.82 (2H, m), 3.70 (3H, s, $-CO_2Me$), 3.76 (1H, q, $J=6.5$ Hz, Me-C*H*(Ar)-NH–), 3.91 (4H, br m, $-OCH_2CH_2O-$), 7.22–7.36 (5H, m, Ar). ν/cm^{-1} (liquid film); 3430 (w), 2960 (s), 1745 (s), 1440 (s), 1360 (s), 1160 (s), 1100 (s), 760 (m), 700 (s). $[\alpha]_D^{30}$ +6 (*c* 0.4, $CHCl_3$). *m*/*z* (EI, %): 347 (1, M^+), 332 (11), 246 (5), 187 (100), 105 (63). $C_{20}H_{29}NO_4$ requires: C, 69.1; H, 8.4; N, 4.0. Found: C, 68.7; H, 8.3; N, 3.8.

4.1.21. (1′*R*,4a*S*,8a*R*)-3,4,4a,5,7,8,8a-Septahydro-6-[spiro-(2,5-oxa)cyclopentyl]-1-[(1′phenyl)ethyl]quinolin-2(1*H*)-one. A solution of methyl (1′*R*,1*S*,2*R*)-5-[spiro-(2,5-oxa)cyclopentyl]-2-[1′-(phenylethyl)amino]cyclohexanepropionate **15** (5.0 g, 14.4 mmol) in toluene (60 ml) and acetic acid (20 ml) was heated at 70 °C for 15 h before the solvents were removed in vacuo and the residue dissolved in toluene (20 ml). After washing the organic solution successively with sodium bicarbonate solution (satd aq; 20 ml), and water (2×20 ml), the solution was dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification using chromatography (ether) gave the title compound (2.9 g, 64%) as a colourless oil. ^1H NMR (300 MHz, $CDCl_3$); δ 1.21 (1H, t, $J=6.9$ Hz), 1.25–1.72 (5H, m), 1.83–2.02 (3H, m), 2.32–2.60 (4H, m), 2.96–3.03 (1H, m), 3.48 (1H, q, $J=7.8$ Hz), 3.85 (2H, br d, $J=5.5$ Hz, $-OCH_2CH_2-$O–), 3.91 (2H, br d, $J=5.5$ Hz, $-OCH_2CH_2O-$), 5.81 (1H, q, $J=7.2$ Hz, Me-C*H*(Ar)-NH–), 7.21–7.39 (5H, m, Ar). ν/cm^{-1} (liquid film) 2950 (m), 1630 (s), 1440 (m), 1380 (w), 1130 (s), 1100 (s), 945 (w), 700 (m). $[\alpha]_D^{30}$ +38 (*c* 0.5, $CHCl_3$). *m*/*z* (EI, %): 315 (83, M^+), 270 (8), 224 (14), 205 (14), 120 (31), 105 (100), 101 (73). $C_{19}H_{25}NO_3$ requires: C, 72.3; H, 8.0; N, 4.4. Found: C, 72.3; H, 8.1; N, 4.3.

4.1.22. (1′*R*,4a*S*,8a*R*)-3,4,4a,5,7,8,8a-Heptahydro-1-[(1′-phenyl)ethyl]quinolin-2,6(1*H*)-dione (16). A solution of (1′*R*, 4a*S*, 8a*R*)-3,4,4a,5,7,8,8a-septa hydro-6-[spiro-(2,5-oxa)cyclopentyl]-1-[(1′phenyl)ethyl]quinolin-2(1*H*)-one (2.5 g, 7.9 mmol) in acetic acid (40 ml) and water (40 ml) was heated at 80 °C for 16 h before the solvents were removed in vacuo and the residue dissolved in ether (20 ml). After washing the organic layer successively with sodium bicarbonate solution (satd aq; 20 ml) and water (2×20 ml), the solution was dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification using chromatography (ether) gave the title compound (1.77 g, 82%) as a colourless oil. ^1H NMR (300 MHz, $CDCl_3$); δ 1.25–1.44 (1H, m), 1.63 (3H, d, $J=7.3$ Hz, *Me*-CH(Ar)–NH–), 1.76 (1H, t, $J=7.9$ Hz), 1.98–2.08 (1H, m), 2.14–2.32 (5H, m), 2.41–2.48 (1H, m), 2.55–2.61 (2H, m), 3.41–3.45 (1H, m), 6.04 (1H, q, $J=$ 7.1 Hz, Me-C*H*(Ar)-NH–), 7.27–7.44 (5H, m, Ar). ν/cm^{-1} (liquid film) 2960 (s), 1715 (s), 1625 (s), 1445 (m), 1285 (m), 1205 (m), 700 (m). $[\alpha]_D^{30}$ +33 (*c* 0.6, $CHCl_3$). *m*/*z* (EI, %): 271 (100, M^+), 256 (7), 174 (20), 160 (34), 105 (90). $^{12}C_{16}C^{13}H_{21}NO_2$ requires: 272.160584. Found: 272.161027.

4.1.23. Dimethyl[4-(3-trifluoromethyl-3*H*-diazirin-3-yl) phenyl]methyl phosphonate (18). A solution of 3-(α-iodo-4-tolyl)-3-(trifluoromethyl)-3*H*-diazirine (**17**) (0.500 g, 1.53 mmol) in toluene (10 ml) and trimethylphosphite (2 ml,

17.0 mmol) was stirred under argon at room temperature for 15 h. After stirring for a further 2 h at 75 °C, the solution was concentrated in vacuo and the residue purified using preparative TLC ($CHCl_3$/MeOH; 5:1) to give the title compound (0.077 g, 18%) as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$); δ 3.17 (2H, d, $J=22.0$ Hz, Ar-CH_2-P), 3.68 (6H, d, $J=10.9$ Hz, (MeO)$_2$P), 7.15 (2H, d, $J=8.0$ Hz, Ar), 7.33 (2H, dd, $J=8.4$, 2.2 Hz, Ar). ν/cm^{-1} (liquid film); 2950 (m), 2920 (m), 1610 (w), 1340 (m), 1230 (s), 1185 (s), 1155 (s), 1030 (s), 935 (m). *m/z* (%): 309 (2, M^+), 280 (100), 248 (12), 184 (13), 170 (34), 151 (48), 109 (45), 93 (49). $C_{11}H_{13}F_3N_2O_3P$ requires: 309.061591. Found: 309.062951.

4.1.24. (1′*R*,4a*S*,8a*R*)-3,4,4a,5,7,8,8a-Heptahydro-6-[4-(3-trifluoromethyl-3*H*-diazirin-3-yl)benzylidene]-1-[(1′-phenyl)ethyl]quinolin-2(1*H*)-one (19). To a stirred solution of dimethyl[4-(3-trifluoromethyl-3*H*-diazirin-3-yl)phenyl]methyl phosphonate **18** (50.0 mg, 162 μmol) in THF (0.5 ml) was added NaH (60% dispersion in mineral oil; 7.9 mg, 198 μmol) in one portion, producing an instant black colouration. After stirring at room temperature under argon for 1 h, a solution of (1′*R*,4a*S*,8a*R*)-3,4,4a,5,7,8,8a-heptahydro-1-[(1′-phenyl)ethyl]quinolin-2,6(1*H*)-dione (**16**) (58.6 mg, 0.32 mmol) in THF (1 ml) was added and the mixture stirred for a further 24 h at room temperature, during which time the black colouration faded. The solution was then diluted with Et_2O (10 ml) and washed with H_2O (2×10 ml) before being dried (Na_2SO_4), filtered and concentrated in vacuo. Purification using flash column chromatography (Et_2O) gave the title compound (22.4 mg, 27%) as a viscous yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$); δ 1.23–2.15 (9H, m), 2.26–2.83 (4H, m), 3.09–3.20 (2H, m), 5.93 (1H, m, Me-C*H*(Ar)-NH–), 6.19 and 6.34 (1H, s, Ar-C*H*=C–, E/Z), 7.06–7.20 (4H, m, Ar), 7.28–7.40 (5H, m, Ar). ν/cm^{-1} (liquid film); 2920 (s), 1740 (w), 1720 (w), 1635 (m), 1615 (s), 1350 (m), 1185 (s), 1160 (s), 935 (m), 700 (m). $[\alpha]_D^{30}$ −28 (*c* 0.1, $CHCl_3$). *m/z* (EI, %): 453 (12, M^+), 427 (5), 331 (5), 209 (7), 149 (12), 120 (19), 105 (100). $C_{26}H_{26}F_3N_3O$ requires: 453.202797. Found: 453.200569.

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