Concise synthesis of bicyclic aminals and their evaluation as precursors to the sarain core

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A number of bicyclic aminals have been prepared in a stereospecific manner as potential precursors to the core structure of the sarain alkaloids. Rearrangement of these aminals to new diazabicyclic and diazatricyclic systems has been observed under various conditions.

Introduction

Sarains A (**1**), B (**2**) and C (**3**) (Fig. 1) are alkaloids with an unprecedented polycyclic structure which were isolated from a Bay of Naples sponge, *Reniera sarai*, in the mid 1980s.[1] Common to the three alkaloids is a diazatricyclic core, which incorporates an unusual "proximity effect" between a tertiary amine and an aldehyde.

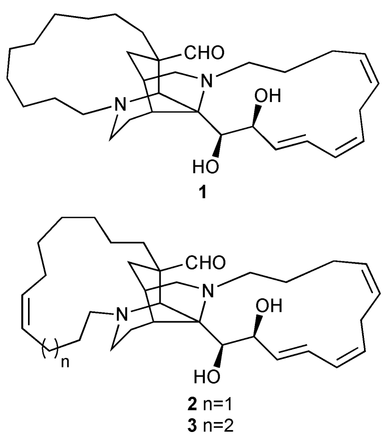

Fig. 1 The sarain alkaloids.

The sarains have attracted significant attention as synthetic targets; five groups have reported syntheses of the core structure,[2,3] and a total synthesis of sarain A has been reported by Overman *et al.*[3]

Our projected approaches to the core of the sarain alkaloids are outlined in Scheme 1. The tricyclic target **4** should be obtainable by a transannular cyclisation of zwitterion **5**; this, in turn would arise from heterolytic C–N bond cleavage in an ammonium ylid, **6** (alternatively, a homolytic mechanism, proceeding through an intermediate diradical, could be envisaged for the conversion of **6** to **4**). Ammonium ylid **6** would be obtained through the reaction of a metal carbenoid, derived from diazoketone **7**, with the more nucleophilic of the two nitrogen atoms of the aminal moiety.

A related approach would be to prepare the tricycle **4** by cyclisation of the silyl enol ether moiety of **8** onto the iminium ion.

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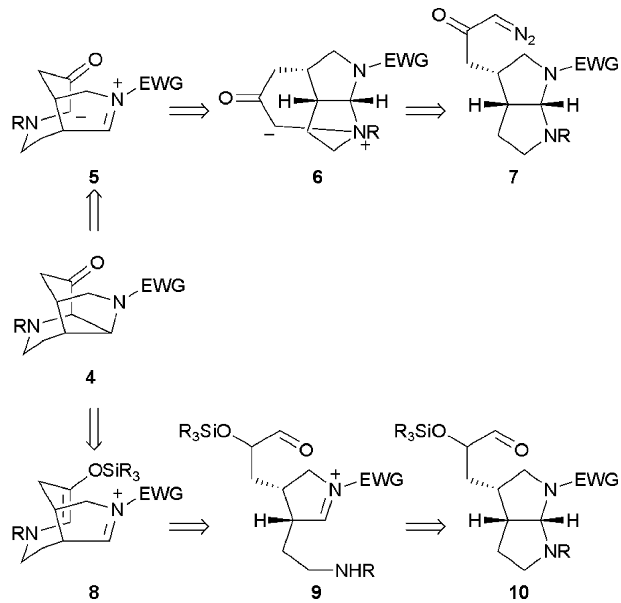


Scheme 1 Retrosynthesis of the sarain core.

Recognising that **8** is not only an enol ether but also an enamine, we can envisage its preparation through intramolecular condensation of a secondary amine with an aldehyde in an intermediate such as **9**; this would in turn arise through protonation and ring-opening of bicyclic aminal **10**.

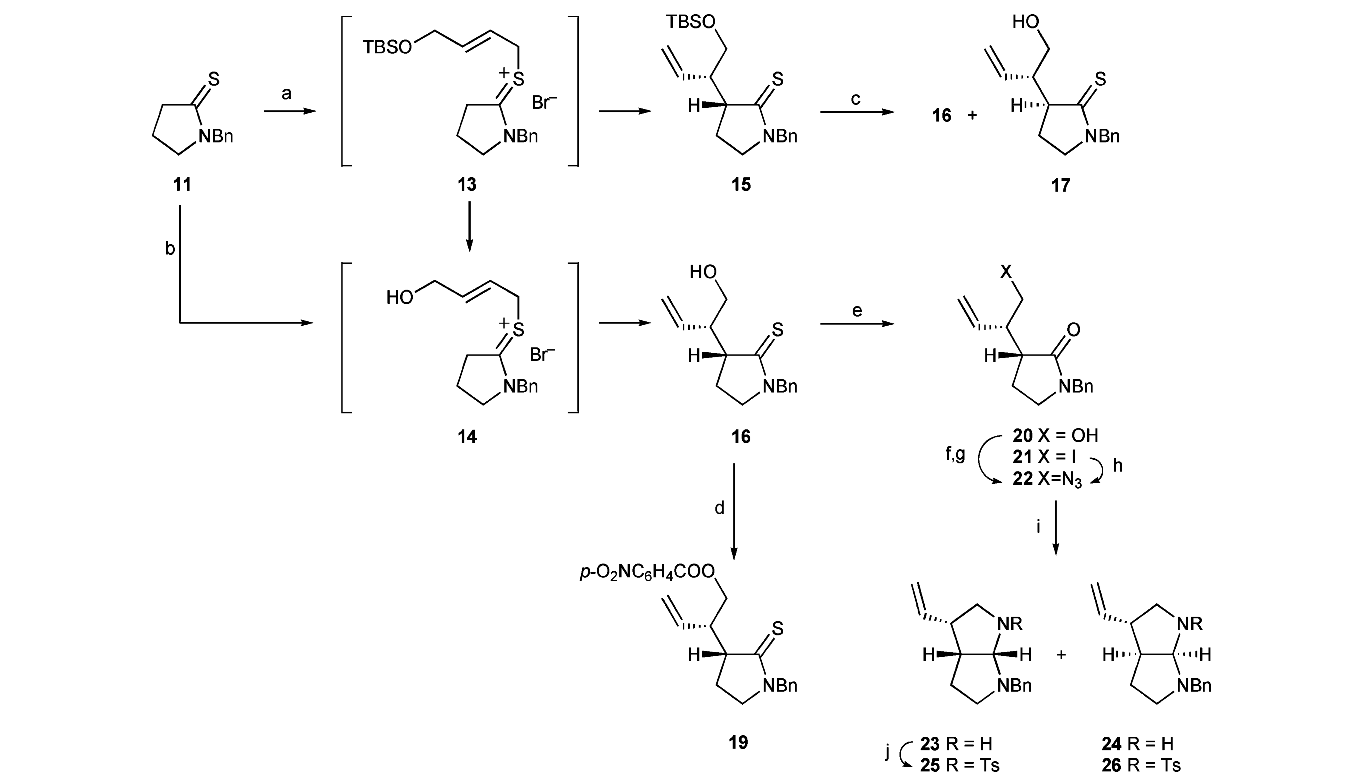
As both potential routes involve bicyclic aminals bearing a substituent on the *endo*-face, the initial task was to develop a method for the synthesis of such compounds.[4]

Results and discussion

Synthesis of bicyclic aminals

The route adopted for the establishment of the correct relative stereochemistry in **7** and **10** was based on the Claisen rearrangement of *N*,*O*- or *N*,*S*-ketene acetals derived from pyrrolidin-2-one. While the use of an *N*,*O*-ketene acetal, as described by Stevenson *et al.*,[5] gave the desired product with good stereoselectivity,[4] we were unable to obtain high yields and thus chose to explore instead the use of *N*,*S*-ketene acetals.[6]

1-Benzylpyrrolidine-2-thione **11**[7] was alkylated with 4-(*tert*-butyldimethylsilyloxy)crotyl bromide **12**[8] to afford the salt **13** as



Scheme 2 Preparation of bicyclic aminals. (a) (*E*)-TBSOCH$_2$CH=CHCH$_2$Br (**12**), CH$_2$Cl$_2$, 3 h then Et$_3$N, CH$_2$Cl$_2$, 16 h, 22% **15** + 22% **16**; (b) (*E*)-HOCH$_2$CH=CHCH$_2$Br (**18**), MeCN, 3 d then Et$_3$N, 40 °C, 2 h, 67%; (c) TBAF, THF, 3 d, 84% **17**; (d) *p*-O$_2$NC$_6$H$_4$COCl, pyridine, 82%; (e) MeI, K$_2$CO$_3$, THF, H$_2$O, 69% **20** + 9% **21**; (f) MsCl, Et$_3$N, CH$_2$Cl$_2$, 0 °C, 99%; (g) NaN$_3$, DMSO, 60 °C, 83%; (h) NaN$_3$, DMSO, 60 °C, 75%; (i) Bu$_3$P, THF then LiAlH$_4$, 77% **23** after alumina column; (j) TsCl, *i*-Pr$_2$NEt, CH$_2$Cl$_2$ then scavenge with polymer-bound tris(2-aminoethyl)amine, 77% **25**.

a *ca.* 2 : 1 mixture with its desilylated analogue **14** (Scheme 2). Upon treatment of this mixture with triethylamine, deprotonation, thia-Claisen rearrangement and further partial deprotection took place to give thiolactams **15** and **16**, each in 22% yield (see below for confirmation of the stereochemical assignment). Attempts to convert **15** into **16** by deprotection with tetra-*n*-butylammonium fluoride (TBAF) were unsuccessful as epimerisation also took place, leading to a 1 : 4.7 mixture of **16** and its diastereomer **17**, from which **17** could be isolated in 84% yield. The same 1 : 4.7 mixture was obtained when pure **16** was treated with TBAF, indicating that it was indeed the basic fluoride ion that was causing the loss of stereochemical integrity. The fact that **15** and **16** have the same relative stereochemistry, as shown, was proved by the reaction of **16** with *tert*-butyldimethylsilyl chloride to afford **15**.

As the *tert*-butyldimethylsilyl group had proven to be labile under the alkylation and deprotonation conditions, we decided to dispense with the protecting group and to carry out the alkylation–rearrangement using the free alcohol **18**.[9]

Following extensive experimentation, it was found that the optimal conditions for the preparation of **16** consisted of stirring a concentrated solution of bromide **18** and thiolactam **11** in acetonitrile for 3 d, before dilution with further acetonitrile, heating to 40 °C, and addition of triethylamine. Under these conditions, **16** and **17** were produced in a >50 : 1 ratio (determined from ^{1}H NMR of the crude reaction mixture), and **16** could be isolated in 67% yield. If the rearrangement was carried out at a higher temperature, a less diastereoselective reaction, with more side products, was observed.

The stereochemistry of thiolactam **16** was confirmed by X-ray crystallography of its *p*-nitrobenzoate **19**,† which showed the relative configuration to be, as expected, that arising from a chair transition state in the thia-Claisen step (Fig. 2).

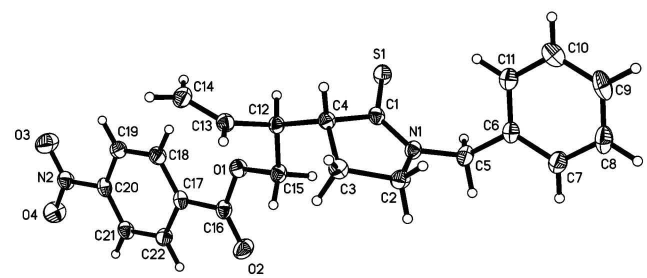


Fig. 2 Thermal ellipsoid plot of **19**. Ellipsoids are drawn at 50% probability level and the H atoms have an arbitrary radius.

Hydrolysis of thiolactam **16** to the corresponding lactam **20** was effected with methyl iodide and potassium carbonate in aqueous tetrahydrofuran; the expected alcohol product was accompanied by a small amount of iodide **21**. Both compounds were then converted to azide **22**.

Cyclisation of azide **22** to a bicyclic aminal was carried out using the tri-*n*-butylphosphine–lithium aluminium hydride protocol previously developed within the group.[4] Analysis of the crude

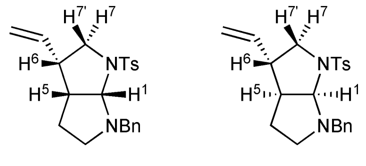
† CCDC reference number 681439. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b806031b

reaction mixture indicated that the stereochemical integrity of the azide had been maintained, and that aminal **23** was present in >98% de. However, following chromatography on silica gel, the isolated product was an inseparable 1 : 3 mixture of the desired *endo*-isomer **23** and *exo*-isomer **24**, formed through acid-catalysed ring-opening and enamine formation, followed by re-protonation and cyclisation.[10] This undesired stereoisomerisation process could be suppressed by conducting chromatography on basic alumina, allowing isolation of aminal **23** in 77% yield.

Tosylation of the secondary amine of **23** afforded sulfonamide **25**, which showed an even greater tendency to stereoisomerisation than **23**; in this case, chromatography even on basic alumina gave a product with substantial contamination by the undesired *exo*-stereoisomer **26** (**25** : **26** = 3.4 : 1). Pure **25** could be obtained only by avoiding chromatography entirely, and instead using a scavenger resin to effect preliminary purification; thus addition of polymer-bound tris(2-aminoethyl)amine to the reaction mixture removed excess tosyl chloride, and **25** was obtained by crystallisation.[11]

The relative stereochemistry of **25** was confirmed by a detailed analysis of ^{1}H-^{1}H coupling constants and nuclear Overhauser enhancements (NOE) in conjunction with molecular mechanics calculations using the MMX force field[12] followed by DFT calculations using the B3LYP/6-31G(d) level of theory.[13] Computational studies allowed prediction of the NOE ratios, dihedral angles and coupling constants for both the *endo*- and *exo*-stereoisomers depicted in Table 1, and comparison with the experimental results clearly indicated that the vinyl group had the desired *endo*-orientation. In particular, on selective excitation of proton 1-H the corresponding enhancement ratio for protons 5-H and 6-H ($\eta_{1\to5}/\eta_{1\to6}$) was found to be 4.5. From the B3LYP/6-31G(d) optimised geometry, the internuclear distances, *r*, between protons 1–5 and 1–6 in **25** are 2.42 Å and 3.09 Å, respectively. Thus using the initial rate approximation,[14] which is based on the r^{-6} dependence of NOEs, the expected enhancement ratio is 4.34. This compares well with the measured value of 4.5.

Table 1 NMR assignment of stereochemistry. The predicted values are for the B3LYP/6-31G(d) optimised geometries. Vicinal $^3J_{HH}$ couplings were predicted using a Karplus-type equation,[15] accounting for the dependence of $^3J_{HH}$ on both the dihedral angle and the substituent electronegativities



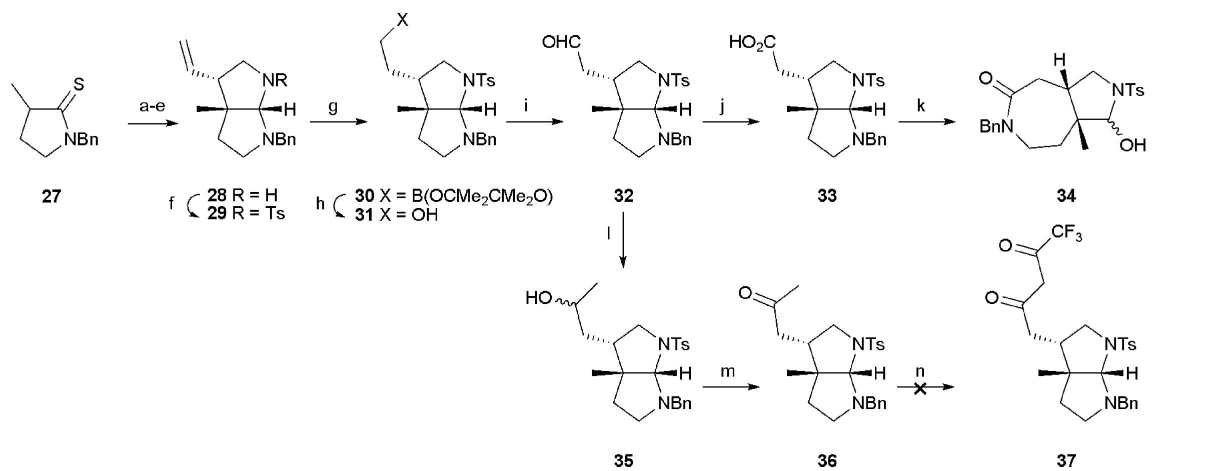
25 **26**

	NOE ratio	Dihedral angles/°		Coupling constants/Hz	
	$\eta_{1\to5}/\eta_{1\to6}$	H^6CCH^7	$H^6CCH^{7'}$	$J_{6,7}$	$J_{6,7'}$
Predicted for **25**	4.3	167	46	11.6	5.8
Predicted for **26**	25.7	90	30	1.2	7.0
Observed	4.5			11.9	6.9

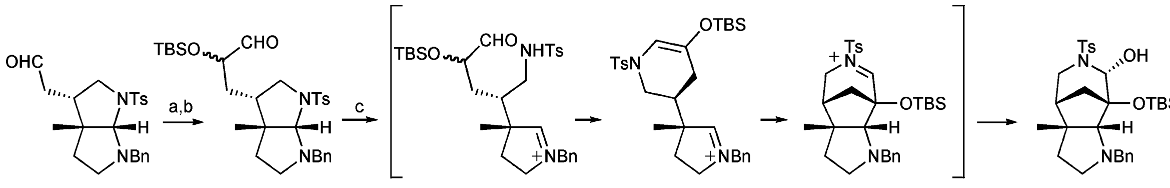
The problems of undesired stereoisomerisation observed in **23** and **25** proved unavoidable in further transformations of these materials, and no subsequent functionalisation of **25** could be carried out without substantial isomerisation occurring. Thus a modification to the strategy was adopted, which would prevent this unwanted process.

It was decided that a "blocking group" should be installed at the junction between the two five-membered rings; this would preclude formation of an enamine and thus stereoisomerisation. While an ideal blocking group would be readily removable at the end of the synthesis, initial studies were carried out using a methyl group as this was felt to be least likely to interfere with the chemistry of interest.

Hence 1-benzyl-3-methylpyrrolidine-2-thione **27** (prepared by thionation of the corresponding lactam[16] with Lawesson's reagent[17]) was carried through an equivalent synthetic sequence to **11** (with minor modifications), to afford bicyclic aminal **28** and thence sulfonamide **29** (Scheme 3). As expected, both **28** and



Scheme 3 Preparation of methylated bicycles. (a) **18**, MeCN, 4 d; Et_3N, 40 °C, 6 h, 75%; (b) *m*CPBA, CH_2Cl_2, 0 °C, 2.5 h, 93%; (c) MsCl, Et_3N, CH_2Cl_2, 0 °C, 1 h; (d) NaN_3, DMSO, 60 °C, 21 h, 87% (2 steps); (e) Bu_3P, THF, rt, 1 h; $LiAlH_4$, 2 h, 75%; (f) TsCl, pyridine, 0 °C to rt, 16 h, 87%; (g) pinacolborane, $(Ph_3P)_3RhCl$, THF, rt, 20 h; (h) $NaBO_3$, H_2O, 0 °C to rt, 5 h, 86% from **29**; (i) Dess–Martin periodinane, pyridine, CH_2Cl_2, 0 °C to rt, 16 h, 80%; (j) $NaClO_2$, KH_2PO_4, 2-methylbut-2-ene, *t*-BuOH, H_2O, 0 °C, 3 h, 85%; (k) *i*-BuOCOCl, Et_3N, THF, −10 °C, 1 h; $TMSCHN_2$, −10 °C to rt, 18 h, <62%; (l) MeMgBr, THF, 0 °C to rt, 3 h, 78%; (m) Dess–Martin periodinane, pyridine, CH_2Cl_2, 0 °C to rt, 5 h, 79%; (n) LiHMDS, THF, −78 °C then $CF_3CO_2CH_2CF_3$, −78 °C to rt.



Scheme 4 Formation of tricycle **42**. (a) TBSCN, LiCl, CH_2Cl_2, rt, 2 d, 88%; (b) DIBAL, toluene, −78 °C, 1.5 h, 42%; (c) AcOH, MeOH, rt to 65 °C, 46 h, 47%.

29 were stereochemically robust, with chromatography on silica proving straightforward.

Attempts to prepare diazoketones

The next task was the conversion of the vinyl group in **29** to either a diazomethyl ketone or a silyloxyaldehyde in order to test the chemistry in Scheme 1. While uncatalysed hydroboration of the alkene proved ineffective, hydroboration with pinacolborane in the presence of Wilkinson's catalyst afforded the boronate **30** in good yield (Scheme 3).[18] This boronate could be isolated and oxidised in a subsequent step, but it proved more convenient to carry out the oxidation to alcohol **31** without prior isolation of **30**. Sodium perborate was the most effective oxidant for this transformation.[19] Further oxidation to aldehyde **32** was effected with Dess–Martin periodinane,[20] and Pinnick oxidation afforded carboxylic acid **33**.[21]

Activation of the carboxylic acid followed by treatment with diazomethane or TMS-diazomethane was then expected to afford the desired diazomethyl ketone; however, on attempted activation of **33** with oxalyl chloride, isobutyl chloroformate, carbonyl diimidazole, DCC–pentafluorophenol or DCC–*N*-hydroxysuccinimide, bicyclic lactam **34** was formed. This compound is presumed to arise from acid-catalysed ring opening of the aminal, cyclisation of the resulting secondary amine onto the activated carboxylic acid, and trapping of the *N*-sulfonyliminium ion with water. All efforts to avoid the acid-catalysed ring opening by carrying out the activation in the presence of a base, or by activation of the sodium or potassium salts of acid **33**, were unsuccessful as lactam **34** was again generated.

An alternative approach to the synthesis of diazomethyl ketones is through the detrifluoroacetylating diazo transfer approach developed by Danheiser *et al.*[22] Conversion of aldehyde **32** to the methyl ketone **36** was carried out through the intermediacy of secondary alcohol **35**; however, all attempts to convert this ketone to the desired diketone **37** were unsuccessful.

Preparation and rearrangement of an α-silyloxyaldehyde

The conversion of bicycle **33** to lactam **34**, while not in itself useful, seemed to indicate that acid-catalysed ring-opening of the bicyclic aminal framework through cleavage of the C–NBn bond was a very straightforward process. Hence conversion of a compound such as **10**, through the ring-opened form **9** to enamine **8** (Scheme 1) was also expected to proceed readily.

In our efforts to synthesise compounds with the structure **10**, we chose to exploit cyanohydrin chemistry. Thus aldehyde **32** was reacted with *tert*-butyldimethylsilyl cyanide and lithium chloride to afford a silylated cyanohydrin as a mixture of diastereomers,[23] and reduction of the nitrile to aldehyde **38** was carried out with DIBAL (Scheme 4).

Aldehyde **38** was subjected to a variety of acidic conditions (acetic acid, *p*-toluenesulfonic acid, trifluoromethanesulfonic acid, Dowex-50, hydrochloric acid) in a number of solvents (methanol, dichloromethane, 1,4-dioxane, water). From none of these reactions could any of the desired tricyclic product be isolated or identified; however, a different tricyclic system **42** could be isolated in moderate yield from the reaction of **38** with acetic acid in methanol at 65 °C for an extended period. This product clearly arises through opening of the aminal system in the undesired direction—through heterolysis of the C–NTs bond rather than the C–NBn bond—giving iminium ion **39**. Reaction of the sulfonamide with the aldehyde could then form a six-membered cyclic enesulfonamide **40**, which would react with the iminium ion to give **41** and, after hydration, the observed tricycle **42**. Alternatively, it may be the enol tautomer of **39** which cyclises in a Mannich reaction, with subsequent hemiaminal formation by cyclisation of the sulfonamide onto the product aldehyde.

While it is conceivable that the processes leading to the formation of **42** are reversible, and that either **42** or the desired tricycle could be the thermodynamic product of acid-catalysed rearrangement of **38**, we have been unable to identify any conditions under which a compound corresponding to tricycle **4** is formed.

Conclusions

A concise route for the stereospecific construction of bicyclic aminals such as **32** has been developed, using thia-Claisen rearrangement and reductive cyclisation as key steps. While it has not yet been possible to convert these aminals to the desired tricyclic sarain core, other modes of reactivity, generating novel bicyclic and tricyclic structures, have been observed.

Experimental

General procedures

All reactions involving non-aqueous reagents were carried out under argon or nitrogen in flame-dried apparatus. 4-Tolylsulfonyl chloride was recrystallised from toluene–petrol prior to use. Ethyldiisopropylamine and triethylamine were distilled from potassium hydroxide; 2,2,2-trifluoroethyl trifluoroacetate, pyridine and DMSO were distilled from calcium hydride; *t*-BuOH was distilled from magnesium. THF, acetonitrile, toluene and CH_2Cl_2 were dried by passage through alumina columns under nitrogen. All other chemicals were used as obtained from commercial sources. Where petrol is specified, this refers to the fraction that boils in the range 40–60 °C.

Column chromatography was carried out on BDH silica gel (Kieselgel 60) or Acros basic alumina (50–200 micron), deactivated to Brockmann Grade III prior to use.

IR spectra were recorded using a SHIMADZU FT-IR 8700 spectrometer. NMR spectra were recorded on Bruker AMX-300, Bruker AMX-400 or Bruker AVANCE-500 spectrometers. Proton and ^{13}C chemical shifts are reported in parts per million (ppm) and are referenced to the residual solvent signal. Peaks were assigned with the aid of COSY, DEPT-135, HMQC and HMBC analysis where applicable. Proton–proton coupling constants are reported in Hz.

Melting points were measured on a Reichert-Jung THERMOVAR instrument and are uncorrected.

Mass measurements were carried out using VG70-SE or Thermo MAT 900 instruments. Elemental analyses were determined on a Perkin Elmer 2400 CHN elemental analyser.

(3*RS*,2′*SR*)-1-Benzyl-3-[1-(*tert*-butyldimethylsilanyloxy)but-3-en-2-yl]pyrrolidine-2-thione 15. 1-Benzylpyrrolidine-2-thione **11**[7] (102 mg, 0.53 mmol) and bromide **12**[8] (153 mg, 0.58 mmol) were combined, with the addition of the minimum volume of CH_2Cl_2 (0.5 mL) required to give a homogeneous mixture, and the resulting mixture was stirred at room temperature for 3 h. Further CH_2Cl_2 (5 mL) was added, followed by triethylamine (0.11 mL, 0.80 mmol) and the resulting solution was stirred overnight. The mixture was diluted with further CH_2Cl_2 (30 mL) and washed with aqueous citric acid (2% w/v, 2 × 15 mL), dried ($MgSO_4$) and concentrated. Flash chromatography (SiO_2; EtOAc–petrol 3 : 97) afforded the title compound **15** (44 mg, 22%) as a colourless oil; ν_{max}/cm^{-1} (film) 2953, 2928, 2856 (CH), 1639 (C=C), 1504, 1256 (C=S), 1101, 837; δ_H (300 MHz; $CDCl_3$) −0.01 (3H, s, C*H*$_3$Si), 0.04 (3H, s, C*H*$_3$Si), 0.85 (9H, s, C(C*H*$_3$)$_3$), 2.00–2.19 (2H, m, NCH$_2$C*H*$_2$), 3.01 (1H, m, CH$_2$=CHC*H*), 3.27 (1H, m, C*H*C=S), 3.44 (1H, ddd, *J* 11.0, 8.5, 6.4) and 3.53 (1H, ddd, *J* 11.0, 8.6, 6.3 CH$_2$C*H*$_2$N), 3.74 (1H, dd, *J* 10.2, 5.4) and 3.87 (1H, dd, *J* 10.2, 5.8, C*H*$_2$O), 4.89 (1H, d, *J* 14.3, NC*H*HPh), 5.09–5.21 (3H, m, C*H*$_2$=CH and NCH*H*Ph), 5.91 (1H, ddd, *J* 17.3, 10.3, 8.0, C*H*=CH$_2$), 7.29–7.34 (5H, m, Ar*H*); δ_C (125 MHz; $CDCl_3$) −5.4 (Si(*C*H$_3$)$_2$), 18.2 (*C*(CH$_3$)$_3$), 22.9 (NCH$_2$*C*H$_2$), 25.9 (C(*C*H$_3$)$_3$), 48.7 (*C*HCH=CH$_2$), 51.6 (N*C*H$_2$Ph), 52.7 (CH$_2$*C*H$_2$N), 55.8 (*C*HC=S), 63.2 (*C*H$_2$O), 116.8 (CH=*C*H$_2$), 127.9, 128.3, 128.8 (aromatic *C*H), 135.2 (aromatic *C*), 137.5 (*C*H=CH$_2$), 203.3 (*C*=S); *m*/*z* (CI$^+$, CH$_4$) 376 (MH$^+$, 17%), 375 (M$^+$, 24), 318 ([M − ^{t}Bu]$^+$, 35), 191 (75), 91 (100). HRMS found 376.2131. Calc. for $C_{21}H_{34}NOSiS$ (MH$^+$) 376.2130.

Further elution (EtOAc–petrol 1 : 1) afforded alcohol **16** (30 mg, 22%).

(3*RS*,2′*SR*)-1-Benzyl-3-(1-hydroxybut-3-en-2-yl)pyrrolidine-2-thione 16. 1-Benzylpyrrolidine-2-thione **11**[7] (2.33 g, 12.2 mmol) and (*E*)-4-bromobut-2-en-1-ol **18**[9] (2.03 g, 13.4 mmol) were dissolved in MeCN (24 mL) and the mixture was stirred for 3 d. Further MeCN (100 mL) was added and the mixture was warmed to 40 °C. Et_3N (1.87 mL, 13.4 mmol) was added and the resulting mixture was stirred at 40 °C for 2 h. After cooling to room temperature, the mixture was diluted with CH_2Cl_2 (300 mL), washed with aqueous citric acid (2% w/v, 2 × 100 mL), dried ($MgSO_4$) and concentrated. Flash chromatography (SiO_2; EtOAc–petrol 1 : 4) afforded the title compound **16** as a pale yellow oil (2.14 g, 67%); ν_{max}/cm^{-1} (film) 3408br (OH), 2924, 2877 (CH), 1504, 1454, 1078, 1030; δ_H (500 MHz; $CDCl_3$) 1.88 (1H, m) and 2.18 (1H, m, NCH$_2$C*H*$_2$), 2.68 (1H, br s, O*H*), 3.02 (1H, m, CH$_2$=CHC*H*), 3.34 (1H, m, C*H*C=S), 3.41–3.54 (2H, m, CH$_2$C*H*$_2$N), 3.72 (1H, m) and 3.86 (1H, m, C*H*$_2$OH), 4.90 (1H, d, *J* 14.3) and 5.05 (1H, d, *J* 14.3, NC*H*$_2$Ph), 5.10 (1H, dd, *J* 10.3, 1.0) and 5.18 (1H, d, *J* 17.2 CH=C*H*$_2$), 5.64 (1H, ddd, *J* 17.2, 10.3, 8.7, C*H*=CH$_2$), 7.24–7.34 (5H, m, Ar*H*); δ_C (125 MHz; $CDCl_3$) 23.1 (NCH$_2$*C*H$_2$), 49.3 (*C*HCH=CH$_2$), 51.8 (N*C*H$_2$Ph), 52.8 (CH$_2$*C*H$_2$N), 55.1 (*C*HC=S), 62.9 (*C*H$_2$OH), 118.4 (CH=*C*H$_2$), 128.1, 128.3, 128.8 (aromatic *C*H), 134.9 (aromatic *C*), 135.6 (*C*H=CH$_2$), 202.9 (*C*=S); *m*/*z* (CI$^+$, CH$_4$) 290 ([M + C$_2$H$_5$]$^+$, 22%), 262 (MH$^+$, 100), 244 ([M − OH]$^+$, 32), 191 (25). HRMS found 262.1260. Calc. for $C_{15}H_{20}NOS$ (MH$^+$) 262.1266.

(3*RS*,2′*RS*)-1-Benzyl-3-(1-hydroxybut-3-en-2-yl)pyrrolidine-2-thione 17. A solution of thioamide **16** (50 mg, 0.19 mmol) in THF (3 mL) was cooled to 0 °C and TBAF (1 M in THF, 0.23 mmol, 2.3 mL) was added dropwise. The resulting solution was allowed to warm to room temperature and stirred for 72 h. Saturated aqueous $NaHCO_3$ (10 mL) was added and the organic material extracted with EtOAc (3 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated, affording a 4.7 : 1 mixture of thioamides **17** and **16**. Flash chromatography (SiO_2; EtOAc–petrol 1 : 4) afforded the title compound **17** (41 mg, 82%) as a pale yellow oil; (Found C, 68.6; H, 7.35; N, 5.3. Calc for $C_{15}H_{19}NOS$ C, 68.9; H, 7.3; N, 5.4%); ν_{max}/cm^{-1} (film) 3379br (OH), 2924, 2876 (CH), 1512, 1450, 1316; δ_H (300 MHz; $CDCl_3$) 1.90 (1H, m) and 2.10 (1H, m, NCH$_2$C*H*$_2$), 2.39 (1H, br s, OH), 3.13 (1H, m, CH$_2$=CHC*H*), 3.31 (1H, m, CHC=S), 3.48 (2H, app t, *J* 7.3, CH$_2$C*H*$_2$N), 3.66 (1H, dd, *J* 11.0, 6.9) and 3.88 (1H, dd, *J* 11.0, 6.1, C*H*$_2$OH), 4.87 (1H, d, *J* 14.3, NC*H*HPh), 5.08–5.21 (3H, m, CH=C*H*$_2$ and NCH*H*Ph), 5.66 (1H, ddd, *J* 17.6, 10.1, 7.8, C*H*=CH$_2$), 7.26–7.31 (5H, m, Ar*H*); δ_C (75 MHz; $CDCl_3$) 21.9 (NCH$_2$*C*H$_2$), 48.3 (*C*HCH=CH$_2$), 51.8 (N*C*H$_2$Ph), 52.7 (CH$_2$*C*H$_2$N), 54.8 (*C*HC=S), 63.9 (*C*H$_2$OH), 118.9 (CH=*C*H$_2$), 128.0, 128.3, 128.8 (aromatic *C*H), 135.0 (aromatic *C*), 135.1 (*C*H=CH$_2$), 203.8 (*C*=S); *m*/*z* (FAB$^+$) 262 (MH$^+$, 100%), 244 ([M − OH]$^+$, 20), 228 (21), 207 (21), 191 (44). HRMS found 262.1267. Calc. for $C_{15}H_{20}NOS$ (MH$^+$) 262.1266.

(3*RS*,2′*SR*)-1-Benzyl-3-[1-(4-nitrobenzoyloxy)but-3-en-2-yl]pyrrolidine-2-thione 19. To a solution of alcohol **16** (100 mg, 0.38 mmol) in pyridine (1.5 mL) at 0 °C was added *para*-nitrobenzoyl chloride (142 mg, 0.77 mmol). The resulting mixture was allowed to warm to room temperature and stirred for 18 h, then diluted with CH_2Cl_2 (30 mL). The solution was washed successively with saturated aqueous $CuSO_4$ (2 × 20 mL), aqueous HCl (1 M, 20 mL), saturated aqueous $NaHCO_3$ (20 mL) and brine (20 mL); it was then dried ($MgSO_4$) and concentrated. Flash chromatography (SiO_2; EtOAc–petrol 3 : 17) afforded the ester **19** (125 mg, 75%) as a yellow solid; mp 113 °C (from CH_2Cl_2–petrol); ν_{max}/cm^{-1} (KBr disc) 2868 (CH), 1719 (C=O), 1522 (NO$_2$), 1346 (NO$_2$), 1273; δ_H (300 MHz; $CDCl_3$) 1.90 (1H, m) and 2.23 (1H, m, NCH$_2$C*H*$_2$), 3.29 (1H, m, CH$_2$=CHC*H*), 3.41–3.57 (3H, m, CH$_2$C*H*$_2$N and C*H*C=S), 4.59–4.64 (2H, m, C*H*$_2$O), 4.93 (1H, d, *J* 14.3) and 5.01 (1H, d, *J* 14.3, NC*H*$_2$Ph), 5.19 (1H, d, *J* 10.4) and 5.26 (1H, dt, *J* 17.2, 1.2, CH=C*H*$_2$), 5.87 (1H, ddd, *J* 17.2, 10.4, 8.1, C*H*=CH$_2$), 7.28–7.35 (5H, m, Ar*H*), 8.17–8.29 (4H, m, Ar*H*); δ_C (75 MHz; $CDCl_3$) 22.7 (NCH_2*C*H_2), 45.5 (CH_2=CH*C*H), 51.8, 52.4 (CH_2*C*H_2N and N*C*H_2Ph), 55.4 (*C*HC=S), 65.3 (*C*H_2O), 118.4 (CH=*C*H_2), 123.5 (aromatic *C*H *o*- to C=O), 128.1, 128.3, 128.9 (aromatic *C*H), 130.8 (aromatic *C*H *o*- to NO_2), 134.9, 135.6 (aromatic *C*), 135.7 (*C*H=CH_2), 150.6 (aromatic *C*), 164.6 (*C*=O), 201.9 (*C*=S); *m/z* (EI) 410 (M^+, 7%), 244 (68), 243 (77), 242 (65), 241 (67), 167 (32), 152 (48), 150 (62), 91 (100). HRMS found 410.1311. Calc. for $C_{22}H_{22}N_2O_4S$ (M^+) 410.1300.

A single crystal suitable for X-ray diffraction was obtained by slow diffusion of petrol into an EtOAc solution of **19**.†

(3*RS*,2′*SR*)-1-Benzyl-3-(1-hydroxybut-3-en-2-yl)pyrrolidin-2-one 20 and (3*RS*,2′*SR*)-1-benzyl-3-(1-iodobut-3-en-2-yl)pyrrolidin-2-one 21. To a stirred solution of thioamide **16** (1.50 g, 5.75 mmol) in THF (50 mL) were added water (10 mL), potassium carbonate (1.59 g, 11.5 mmol) and MeI (1.78 mL, 28.8 mmol) and the resulting mixture was stirred at room temperature for 1 week. The reaction mixture was diluted with CH_2Cl_2 (200 mL) and washed with water (2 × 100 mL), dried ($MgSO_4$) and concentrated. Purification by flash chromatography (SiO_2; EtOAc–petrol 1 : 1) afforded the iodide **21** (185 mg, 9%) as a yellow oil; (Found C, 50.9; H, 5.3; N, 3.8. Calc. for $C_{15}H_{18}INO$: C 50.7, H 5.1, N 3.9%); ν_{max}/cm^{-1} (film) 2945 (CH), 1682br (C=O), 1433br; δ_H (500 MHz; $CDCl_3$) 1.75 (1H, m) and 2.08 (1H, m, NCH_2C*H_2*), 2.56 (1H, m, CH_2=CHC*H*), 2.89 (1H, td, *J* 9.0, 3.3, C*H*C=O), 3.11–3.17 (2H, m, CH_2C*H_2*N), 3.41 (1H, dd, *J* 9.7, 7.1) and 3.72 (1H, dd, *J* 9.7, 7.6, C*H_2*I), 4.35 (1H, d, *J* 14.6) and 4.45 (1H, d, *J* 14.6, NC*H_2*Ph), 5.13–5.20 (2H, m, CH=C*H_2*), 5.64 (1H, dt, *J* 17.0, 9.8, C*H*=CH_2), 7.18–7.32 (5H, m, Ar*H*); δ_C (125 MHz; $CDCl_3$) 9.8 (*C*H_2I), 22.4 (NCH_2*C*H_2), 44.6 (*C*HC=O), 44.8 (CH_2*C*H_2N), 46.6 (N*C*H_2Ph), 49.1 (CH_2=CH*C*H), 119.3 (CH=*C*H_2), 127.5, 128.1, 128.6 (aromatic *C*H), 136.32 and 136.34 (*C*H=CH_2 and aromatic *C*), 174.0 (*C*=O); *m/z* (CI$^+$, CH_4) 384 ($[M + C_2H_5]^+$, 6%), 356 (MH^+, 88), 228 ($[M - I]^+$, 100), 175 (34). HRMS found 356.0502. Calc. for $C_{15}H_{19}INO$ (MH^+) 356.0511.

Further elution afforded alcohol **20** (0.97 g, 69%) as a colourless oil; ν_{max}/cm^{-1} (film) 3418br (OH), 2922, 2874 (CH), 1663br (C=O); δ_H (300 MHz; $CDCl_3$) 1.87 (1H, dq, *J* 12.9, 8.6) and 2.10 (1H, m, NCH_2C*H_2*), 2.47 (1H, m, CH_2=CHC*H*), 2.86 (1H, td, *J* 9.1, 3.1, C*H*C=O), 3.18–3.23 (2H, m, CH_2C*H_2*N), 3.76–3.93 (2H, m, C*H_2*OH), 4.35 (1H, br s, O*H*), 4.39 (1H, d, *J* 14.6) and 4.49 (1H, d, *J* 14.6, NC*H_2*Ph), 5.13–5.21 (2H, m, CH=C*H_2*), 5.85 (1H, ddd, *J* 16.9, 10.5, 9.4, C*H*=CH_2), 7.19–7.36 (5H, m, Ar*H*); δ_C (75 MHz; $CDCl_3$) 22.2 (NCH_2*C*H_2), 45.3 (*C*HC=O), 45.6, 47.0 (CH_2*C*H_2N and N*C*H_2Ph), 48.0 (CH_2=CH*C*H), 65.9 (*C*H_2O), 118.9 (CH=*C*H_2), 127.7, 128.1, 128.7 (aromatic *C*H), 135.3 (*C*H=CH_2), 136.1 (aromatic *C*), 175.0 (*C*=O); *m/z* (FAB$^+$) 246 (MH^+, 100%), 228 ($[M - OH]^+$, 7), 154 (13).

(3*RS*,2′*SR*)-3-(1-Azidobut-3-en-2-yl)-1-benzylpyrrolidin-2-one 22. *(i) From alcohol 20.* To a solution of alcohol **20** (108 mg, 0.44 mmol) in CH_2Cl_2 (2 mL) at 0 °C were added Et_3N (0.122 mL, 8.8 mmol) and methanesulfonyl chloride (0.068 mL, 8.8 mmol) dropwise. The resulting solution was stirred at 0 °C for 3 h, then water (10 mL) was added. The organic material was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated. Flash chromatography (SiO_2; EtOAc–petrol 1 : 2) afforded (3*RS*,2′*SR*)-1-benzyl-3-[1-(methanesulfonyloxy)but-3-en-2-yl]pyrrolidin-2-one (130 mg, 91%) as a colourless oil; (Found: C, 59.6; H, 6.7; N, 4.3. Calc. for $C_{16}H_{21}NO_4S$: C, 59.4; H, 6.5; N, 4.3%); ν_{max}/cm^{-1} (film) 2936 (CH), 1682 (C=O), 1356 (SO_2), 1175 (SO_2), 953; δ_H (300 MHz; $CDCl_3$) 1.82 (1H, dq, *J* 13.0, 8.4) and 2.10 (1H, m, NCH_2C*H_2*), 2.73–2.89 (2H, m, CH_2=CHC*H* and C*H*C=O), 3.04 (3H, s, SC*H_3*), 3.15–3.27 (2H, m, CH_2C*H_2*N), 4.38 (1H, d, *J* 14.6, NC*H*HPh), 4.43 (1H, m, C*H*HOMs), 4.46 (1H, d, *J* 14.6, NCH*H*Ph), 4.67 (1H, dd, *J* 9.8, 8.0, CH*H*OMs), 5.24–5.29 (2H, m, CH=C*H_2*), 5.65 (1H, ddd, *J* 17.4, 9.8, 9.1, C*H*=CH_2), 7.19–7.36 (5H, m, Ar*H*); δ_C (75 MHz; $CDCl_3$) 21.9 (NCH_2*C*H_2), 37.2 (S*C*H_3), 41.3 (*C*HC=O), 45.1 (N*C*H_2CH_2), 45.5 (CH_2=CH*C*H), 46.7 (N*C*H_2Ph), 70.6 (*C*H_2OMs), 120.8 (CH=*C*H_2), 127.7, 128.1, 128.7 (aromatic *C*H), 133.3 (*C*H=CH_2), 136.3 (aromatic *C*), 174.1 (*C*=O); *m/z* (CI$^+$, CH_4) 323 (MH^+, 35%), 244 (22), 228 ($[M - OMs]^+$, 51), 174 (100), 118 (13).

To a solution of this mesylate (130 mg, 0.40 mmol) in DMSO (1.5 mL) was added sodium azide (78 mg, 1.21 mmol) and the resulting mixture was heated to 60 °C for 2.5 h. The solution was allowed to cool to room temperature and water (15 mL) was added. The organic material was extracted with EtOAc (3 × 30 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated. Flash chromatography (SiO_2; EtOAc–petrol 1 : 4) afforded the azide **22** (77 mg, 71%) as a colourless oil; (Found: C, 66.4; H, 6.7; N, 20.4. Calc. for $C_{15}H_{18}N_4O$: C, 66.6; H, 6.7; N, 20.7%); ν_{max}/cm^{-1} (film) 2874 (CH), 2097 (N_3), 1682 (C=O); δ_H (300 MHz; $CDCl_3$) 1.79 (1H, dq, *J* 12.9, 8.4) and 2.09 (1H, m, NCH_2C*H_2*), 2.58 (1H, m, CH_2=CHC*H*), 2.75 (1H, td, *J* 9.0, 3.3, C*H*C=O), 3.12–3.21 (2H, m, CH_2C*H_2*N), 3.60 (1H, dd, *J* 12.2, 7.9) and 3.69 (1H, dd, *J* 12.2, 7.1, C*H_2*N_3), 4.36 (1H, d, *J* 14.6) and 4.48 (1H, d, *J* 14.6, NC*H_2*Ph), 5.20–5.25 (2H, m, CH=C*H_2*), 5.71 (1H, ddd, *J* 17.0, 10.3, 9.1, C*H*=CH_2), 7.20–7.35 (5H, m, Ar*H*); δ_C (125 MHz; $CDCl_3$) 21.8 (NCH_2*C*H_2), 42.5 (*C*HC=O), 44.9 (N*C*H_2CH_2), 45.7 (CH_2=CH*C*H), 46.5 (N*C*H_2Ph), 52.8 (*C*H_2N_3), 119.3 (CH=*C*H_2), 127.5, 128.0, 128.6 (aromatic *C*H), 135.5 (*C*H=CH_2), 136.3 (aromatic *C*), 174.1 (*C*=O); *m/z* (FAB$^+$) 271 (MH^+, 100%), 243 ($[MH - N_2]^+$, 5), 228 ($[M - N_3]^+$, 7), 215 ($[M - CH_2N_3]^+$, 18).

(ii) From iodide 21. To a solution of iodide **21** (237 mg, 0.67 mmol) in DMSO (3 mL) was added sodium azide (130 mg, 2.0 mmol) and the resulting mixture stirred at 60 °C for 3 h. The mixture was allowed to cool to room temperature, water (30 mL) was added and the organic material extracted with EtOAc (3 × 40 mL). The combined organic extracts were washed with brine (80 mL), dried ($MgSO_4$) and concentrated. Flash chromatography (SiO_2; EtOAc–petrol 15 : 85) afforded the azide **22** as a colourless oil (135 mg, 75%).

(1*RS*,5*RS*,6*SR*)-2-Benzyl-6-vinyl-2,8-diazabicyclo[3.3.0]octane 23. To a solution of azide **22** (100 mg, 0.37 mmol) in THF (3 mL) was added tributylphosphine (0.11 mL, 0.44 mmol) and the resulting mixture was stirred at room temperature for 1 h. Lithium aluminium hydride (1 M in THF, 0.22 mL, 0.22 mmol) was added dropwise and the resulting mixture was stirred at room temperature for a further 40 min. Aqueous sodium potassium tartrate solution (0.5 M, 10 mL) was added and the mixture was stirred for a further 1 h. Brine (10 mL) was added and the organic material extracted with EtOAc (3 × 15 mL). The combined organic extracts were washed with water (25 mL), brine (25 mL), dried ($MgSO_4$) and concentrated. Flash chromatography (grade III basic Al_2O_3; EtOAc–petrol 1 : 19) afforded the bicycle **23** (65 mg, 77%, 97% de) as a colourless oil; ν_{max}/cm^{-1} (film) 3298br (NH), 2963, 2928, 2866, 2793 (CH), 1639 (C=C), 1450, 914, 698; δ_H (500 MHz; $CDCl_3$) 1.59–1.68 (2H, m, $BnNCH_2CH_2$), 1.89 (1H, br s, N*H*), 2.31 (1H, app q, *J* 8.0, NC*H*HCH_2), 2.61 (1H, m, C*H*$CH{=}CH_2$), 2.68 (1H, app quintet, *J* 8.1, NCHNC*H*), 2.76–2.80 (2H, m, BnNCH*H*CH_2 and NHC*H*H), 2.87 (1H, dd, *J* 10.2, 6.4, NHCH*H*), 3.65 (1H, d, *J* 13.0) and 3.84 (1H, d, *J* 13.0, NCH_2Ph), 4.14 (1H, d, *J* 7.0, NC*H*N), 5.02–5.06 (2H, m, $CH{=}CH_2$), 5.83 (1H, ddd, *J* 17.6, 10.2, 7.1, C*H*$=CH_2$), 7.20–7.32 (5H, m, Ar*H*); δ_C (125 MHz; $CDCl_3$) 24.7 (NCH_2CH_2), 45.7 (NCHNCH), 47.8 ($CHCH{=}CH_2$), 49.0 ($NHCH_2$), 52.4 ($BnNCH_2$), 57.5 (NCH_2Ph), 83.6 (NCHN), 115.9 ($CH{=}CH_2$), 126.8, 128.2, 128.9 (aromatic *C*H), 136.6 ($CH{=}CH_2$), 139.4 (aromatic *C*); *m/z* (EI$^+$) 228 (M$^+$, 48%), 198 (50), 158 (17), 108 (50), 91 (100). HRMS found 228.1424. Calc. for $C_{15}H_{20}N_2$ (MH$^+$) 228.1626.

(1*RS*,4*SR*,5*RS*)-8-Benzyl-2-(4-tolylsulfonyl)-4-vinyl-2,8-diazabicyclo[3.3.0]octane 25. To a solution of amine **23** (261 mg, 1.14 mmol) in CH_2Cl_2 (8 mL) was added ethyldiisopropylamine (0.59 mL, 3.42 mmol) and the resulting mixture was cooled to 0 °C. 4-Tolylsulfonyl chloride (262 mg, 1.37 mmol) was added and the resulting solution was stirred at 0 °C for 1 h, then allowed to warm to room temperature and stirred for 48 h. Tris(2-aminoethyl)amine-PS (518 mg, active loading 1.1 mmol g^{-1}, 0.57 mmol) was added and the resulting suspension was stirred for 3 h. The mixture was diluted with CH_2Cl_2 (50 mL) and filtered then washed with saturated aqueous $NaHCO_3$ (20 mL) and brine (20 mL), dried ($MgSO_4$), and concentrated. Recrystallisation (MeOH–H_2O) afforded the title compound **25** (337 mg, 77%) as white needles; mp 97–98 °C (from MeOH–H_2O); (Found C, 69.4; H, 7.0; N, 7.1. Calc. for $C_{22}H_{26}N_2O_2S$: C, 69.1; H 6.85; N 7.3%); ν_{max}/cm^{-1} (KBr disc) 2928, 2810 (CH), 1641 (C=C), 1333 (SO_2), 1159 (SO_2), 1088, 885, 833, 715; δ_H (500 MHz; $CDCl_3$) 1.59–1.65 (2H, m, $BnNCH_2CH_2$), 2.18 (1H, m, C*H*$CH{=}CH_2$), 2.43 (3H, s, CH_3), 2.49 (1H, dt, *J* 9.1, 6.8) and 2.62 (1H, dt, *J* 9.1, 6.2, $BnNCH_2CH_2$), 2.73 (1H, app quintet, *J* 7.9, NCHNC*H*), 3.16 (1H, t, *J* 12.0) and 3.61 (1H, dd, *J* 12.1, 6.9, $TsNCH_2$), 4.04 (1H, d, *J* 13.9) and 4.07 (1H, d, *J* 13.9, NCH_2Ph), 4.91 (1H, dt, *J* 17.4, 1.5) and 5.05 (1H, dt, *J* 10.6, 1.4, $CH{=}CH_2$), 5.14 (1H, d, *J* 6.7, NC*H*N), 5.64 (1H, ddd, *J* 17.4, 10.6, 6.5, C*H*$=CH_2$), 7.21–7.29 (7H, m) and 7.74–7.76 (2H, m, Ar*H*); δ_C (125 MHz; $CDCl_3$) 21.5 ($ArCH_3$), 24.0 (NCH_2CH_2), 45.0 ($CHCH{=}CH_2$), 46.2 (NCHNCH), 50.7 ($BnNCH_2$), 50.9 ($TsNCH_2$), 55.5 (NCH_2Ph), 84.9 (NCHN), 117.2 ($CH{=}CH_2$), 126.7, 127.2, 128.6, 128.8, 129.8 (aromatic *C*H), 134.6 ($CH{=}CH_2$), 137.2, 139.1, 143.3 (aromatic *C*); *m/z* (CI$^+$) 383 (MH$^+$, 3%), 227 ([M − Ts]$^+$, 28), 199 (100), 158 (12), 108 (14). HRMS found 383.1788. Calc. for $C_{22}H_{27}N_2O_2S$ (MH$^+$) 383.1793.

1-Benzyl-3-methylpyrrolidine-2-thione 27. A solution of 1-benzyl-3-methylpyrrolidin-2-one[16] (16.2 g, 85.6 mmol) and Lawesson's reagent[17] (20.8 g, 51.4 mmol) in THF (400 mL) was heated at 40 °C for 2 h. After cooling to room temperature, the reaction mixture was quenched by addition of H_2O (250 mL), then stirred for 10 min. The organic products were extracted with EtOAc (3 × 200 mL), and the combined extracts were washed with brine (250 mL), dried ($MgSO_4$) and concentrated. Filtration through a short column of flash silica, eluting with EtOAc–petrol 2 : 3, removed the polar impurities. Further purification by flash chromatography (SiO_2; EtOAc–petrol 1 : 19 → 1 : 9) provided thioamide **27** (16.0 g, 91%) as a pale yellow oil; ν_{max}/cm^{-1} (film) 2966, 2927, 2872 (CH), 1452, 1232 (C=S); δ_H (400 MHz; $CDCl_3$) 1.39 (3H, d, *J* 7.0, CH_3), 1.62 (1H, m) and 2.27 (1H, m, $BnNCH_2CH_2$), 2.95 (1H, m, C*H*Me), 3.40–3.55 (2H, m, $BnNCH_2$), 4.95 (1H, d, *J* 14.5) and 5.04 (1H, d, *J* 14.5, NCH_2Ph), 7.24–7.38 (5H, m, Ar*H*); δ_C (75 MHz; $CDCl_3$) 19.5 (CH_3), 28.3 ($BnNCH_2CH_2$), 48.9 (*C*HMe), 51.8 and 51.9 ($PhCH_2NCH_2$), 128.0, 128.2, 128.8 (aromatic *C*H), 135.2 (aromatic *C*), 206.7 (*C*=S); *m/z* (CI$^+$) 234 ([M + C_2H_5]$^+$, 23%), 206 (MH$^+$, 100). HRMS found 206.1005. Calc. for $C_{12}H_{16}NS$ (MH$^+$) 206.1003.

(1*RS*,5*RS*,6*SR*)-2-Benzyl-5-methyl-6-vinyl-2,8-diazabicyclo[3.3.0]octane 28.

(3RS,2′SR)-1-Benzyl-3-(1-hydroxybut-3-en-2-yl)-3-methylpyrrolidine-2-thione. A solution of 1-benzyl-3-methylpyrrolidine-2-thione **27** (13.6 g, 66.4 mmol) and (*E*)-4-bromobut-2-en-1-ol **18**[9] (11.2 g, 74.3 mmol) in MeCN (10 mL) was stirred at room temperature for 4 d. After dilution with further MeCN (350 mL), the mixture was heated to 40 °C then Et_3N (10.2 mL, 73.1 mmol) was added. After 6 h, the mixture was cooled to room temperature, diluted with CH_2Cl_2 (750 mL) and washed with aqueous citric acid (10% w/v, 2 × 150 mL) and brine (150 mL), and dried ($MgSO_4$). Concentration and purification by flash chromatography (SiO_2; EtOAc–petrol 1 : 9 → 3 : 7) afforded the title thiolactam (13.7 g, 75%) as a pale yellow solid; mp 49–50 °C; (Found C, 69.6; H, 7.9; N, 5.0. Calc. for $C_{16}H_{21}NOS$: C, 69.8; H, 7.7; N, 5.1%); ν_{max}/cm^{-1} (KBr disc) 3337br (OH), 2872 (CH), 1504, 1448, 1232 (C=S); δ_H (400 MHz; $CDCl_3$) 1.23 (3H, s, CH_3), 1.74 (1H, ddd, *J* 12.8, 8.0, 4.7, $BnNCH_2$C*H*H), 1.90 (1H, br dd, *J* 6.6, 3.8, O*H*), 2.16 (1H, ddd, *J* 12.8, 9.1, 8.0, $BnNCH_2$CH*H*), 2.93 (1H, dt, *J* 9.9, 6.6, C*H*CH_2OH), 3.40–3.53 (2H, m, $BnNCH_2$), 3.55–3.70 (2H, m, CH_2OH), 4.99 (1H, d, *J* 14.3) and 5.03 (1H, d, *J* 14.3, NCH_2Ph), 5.24–5.32 (2H, m, $HC{=}CH_2$), 5.64 (1H, dt, *J* 17.0, 9.9, *H*C$=CH_2$), 7.27–7.37 (5H, m, Ar*H*); δ_C (100 MHz; $CDCl_3$) 27.1 (CH_3), 28.6 ($BnNCH_2CH_2$), 51.1 and 52.0 ($PhCH_2NCH_2$), 54.5 ($CHCH_2OH$), 56.6 (*C*Me), 63.1 (CH_2OH), 120.1 ($HC{=}CH_2$), 128.1, 128.2, 128.9 (aromatic *C*H), 135.1 (aromatic *C*), 135.5 (H*C*$=CH_2$), 208.6 (*C*=S); *m/z* (CI$^+$) 304 ([M + C_2H_5]$^+$, 20%), 276 (MH$^+$, 100), 258 (16), 205 (19). HRMS found 276.1424. Calc. for $C_{16}H_{22}NOS$ (MH$^+$) 276.1422.

(3RS,2′SR)-1-Benzyl-3-(1-hydroxybut-3-en-2-yl)-3-methylpyrrolidin-2-one. To a stirred solution of (3*RS*,2′*SR*)-1-benzyl-3-1-hydroxybut-3-en-2-yl-3-methylpyrrolidine-2-thione (13.7 g, 50.0 mmol) in CH_2Cl_2 (600 mL) at 0 °C was added *m*CPBA (70% by weight, 27.7 g, 112 mmol) in 3 g portions every 10 min. After a further 1 h at 0 °C, the reaction was allowed to warm to room temperature, poured into saturated aqueous $NaHCO_3$ (400 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 400 mL), then the combined organic extracts were dried ($MgSO_4$) and concentrated. Flash chromatography (SiO_2; EtOAc–petrol 4 : 6 → 8 : 2) afforded the title lactam (12.0 g, 93%) as a white solid; mp 53–55 °C; (Found: C, 74.0; H, 8.2; N, 5.3. Calc. for $C_{16}H_{21}NO_2$: C, 74.1; H, 8.2; N, 5.4%); ν_{max}/cm^{-1} (KBr disc) 3371br (OH), 2862 (CH), 1676 (C=O), 1496, 1450; δ_H (500 MHz; $CDCl_3$) 1.23 (3H, s, CH_3), 1.62 (1H, ddd, *J* 12.8, 7.9, 3.5) and 2.13 (1H, dt, *J* 12.8, 8.5, $BnNCH_2CH_2$), 2.26 (1H, dt, *J* 10.0, 4.4, C*H*CH_2OH), 3.10–3.23 (2H, m, $BnNCH_2$),

3.62 (1H, dd, *J* 11.3, 4.4) and 3.90 (1H, ddd, *J* 11.3, 4.4, 1.6, C*H*$_2$OH), 3.97 (1H, br s, O*H*), 4.40 (1H, d, *J* 14.7) and 4.45 (1H, d, *J* 14.7, PhC*H*$_2$), 5.14–5.21 (2H, m, HC=C*H*$_2$), 5.78 (1H, dt, *J* 17.0, 10.0, *H*C=CH$_2$), 7.16–7.35 (5H, m, Ar*H*); δ_C (75 MHz; CDCl$_3$) 22.8 (*C*H$_3$), 29.7 (BnNCH$_2$*C*H$_2$), 44.1 (BnN*C*H$_2$), 46.8 (*C*Me), 47.0 (N*C*H$_2$Ph), 53.1 (*C*HCH$_2$OH), 63.0 (*C*H$_2$OH), 119.2 (HC=*C*H$_2$), 127.7, 128.1, 128.7 (aromatic *C*H), 136.1 (aromatic *C*), 136.2 (H*C*=CH$_2$), 178.8 (*C*=O); *m/z* (CI$^+$) 260 (MH$^+$, 100%), 242 (32), 229 (17), 190 (45), 91 (28). HRMS found 260.1640. Calc. for $C_{16}H_{22}NO_2$ (MH$^+$) 260.1645.

*(3*RS*,2′*SR*)-3-(1-Azidobut-3-en-2-yl)-1-benzyl-3-methylpyrrolidin-2-one.* To a stirred solution of (3*RS*,2′*SR*)-1-benzyl-3-1-hydroxybut-3-en-2-yl-3-methylpyrrolidin-2-one (11.9 g, 45.9 mmol) in CH$_2$Cl$_2$ (150 mL) at 0 °C were added Et$_3$N (12.8 mL, 92 mmol) and methanesulfonyl chloride (7.1 mL, 92 mmol). After 1 h, the reaction was allowed to warm to room temperature, diluted with CH$_2$Cl$_2$ (100 mL), washed successively with H$_2$O (2 × 100 mL) and brine (2 × 100 mL), then dried (MgSO$_4$). Concentration provided the desired mesylate (17.7 g) as a colourless oil which was used without further purification. The oil was dissolved in DMSO (50 mL), NaN$_3$ (8.9 g, 140 mmol) was added and the mixture was stirred at 60 °C for 21 h. The reaction mixture was cooled to room temperature, then diluted with H$_2$O (400 mL) and the organic material extracted with EtOAc (4 × 50 mL). The combined organic extracts were washed with brine (50 mL), dried (MgSO$_4$) and concentrated. Purification by flash chromatography (SiO$_2$; EtOAc–petrol 1 : 9 → 2 : 8) provided the title azide (11.3 g, 87%) as white crystals; mp 40–42 °C; (Found: C, 67.5; H, 7.2; N, 19.4. Calc. for $C_{16}H_{20}N_4O$: C, 67.6; H, 7.1; N, 19.7%); ν_{max}/cm^{-1} (KBr disc) 2968, 2893 (CH), 2085 (N$_3$), 1680 (C=O), 1497, 1433; δ_H (500 MHz; CDCl$_3$) 1.14 (3H, s, C*H*$_3$), 1.60 (1H, ddd, *J* 13.1, 7.8, 3.9) and 2.03 (1H, ddd, *J* 13.1, 8.7, 7.8, BnNCH$_2$C*H*$_2$), 2.53 (1H, td, *J* 9.7, 4.3, C*H*CH$_2$N$_3$), 3.06–3.16 (2H, m, BnNC*H*$_2$), 3.30 (1H, dd, *J* 12.2, 9.7) and 3.44 (1H, dd, *J* 12.2, 4.3, C*H*$_2$N$_3$), 4.40 (1H, d, *J* 14.7) and 4.43 (1H, d, *J* 14.7, NC*H*$_2$Ph), 5.23–5.28 (2H, m, HC=C*H*$_2$), 5.57 (1H, dt, *J* 17.4, 9.7, *H*C=CH$_2$), 7.14–7.34 (5H, m, Ar*H*); δ_C (125 MHz; CDCl$_3$) 23.2 (*C*H$_3$), 28.1 (BnNCH$_2$*C*H$_2$), 43.3 (BnN*C*H$_2$), 45.7 (*C*Me), 46.8 (N*C*H$_2$Ph), 50.2 (*C*HCH$_2$N$_3$), 51.6 (*C*H$_2$N$_3$), 120.2 (HC=*C*H$_2$), 127.6, 128.1, 128.7 (aromatic *C*H), 135.2 (H*C*=CH$_2$), 136.3 (aromatic *C*), 177.1 (*C*=O); *m/z* (CI$^+$) 285 (MH$^+$, 43%), 257 (67), 242 (100), 228 (35), 188 (18), 152 (22), 117 (21). HRMS found 285.1706. Calc. for $C_{16}H_{21}N_4O$ (MH$^+$) 285.1710.

*(1*RS*,5*RS*,6*SR*)-2-Benzyl-5-methyl-6-vinyl-2,8-diazabicyclo[3.3.0]octane* ***28***. A solution of (3*RS*,2′*SR*)-3-(1-azidobut-3-en-2-yl)-1-benzyl-3-methylpyrrolidin-2-one (2.00 g, 7.0 mmol) and tributylphosphine (3.2 mL, 12.7 mmol) in THF (60 mL) was stirred at room temperature for 1 h then LiAlH$_4$ (0.27 g, 7.0 mmol) was slowly added. After 1 h, further LiAlH$_4$ (0.27 g, 7.0 mmol) was added and stirring was continued for a further 1 h. After quenching by addition of aqueous sodium potassium tartrate (0.5 M, 60 mL) the mixture was stirred for 30 min. The product was then extracted with EtOAc (3 × 60 mL), washed with H$_2$O (2 × 60 mL) and brine (2 × 60 mL), then dried (MgSO$_4$) and concentrated. The residue was redissolved in CH$_2$Cl$_2$ (20 mL) and the amine product extracted with 2 M HCl (3 × 20 mL). The combined aqueous extracts were cooled in an ice bath and basified to pH 11 with 3 M NaOH. The organic material was extracted with EtOAc (3 × 50 mL), washed with brine (50 mL), dried (MgSO$_4$) and concentrated. Flash chromatography (SiO$_2$; MeOH–CH$_2$Cl$_2$ 1 : 49 → 1 : 9) provided the bicycle **28** (1.27 g, 75%) as a pale yellow oil; δ_H (400 MHz; CDCl$_3$) 1.15 (3H, s, C*H*$_3$), 1.21 (1H, ddd, *J* 12.3, 5.5, 2.0) and 1.82 (1H, ddd, *J* 12.3, 10.4, 7.1, BnNCH$_2$C*H*$_2$), 2.31 (1H, dt, *J* 10.4, 7.4, HNCH$_2$C*H*), 2.47 (1H, m) and 2.84 (1H, m, HNC*H*$_2$), 2.93–3.03 (2H, m, BnNC*H*$_2$), 3.68 (1H, d, *J* 13.0, PhC*H*H), 3.79 (1H, s, NC*H*N), 3.92 (1H, d, *J* 13.0, PhCH*H*), 5.02–5.10 (2H, m, CH=C*H*$_2$), 5.74 (1H, ddd, *J* 17.1, 10.7, 7.4, *H*C=CH$_2$), 7.20–7.37 (5H, m, Ar*H*); δ_C (100 MHz; CDCl$_3$) 25.1 (*C*H$_3$), 32.0 (BnNCH$_2$*C*H$_2$), 49.3 (BnN*C*H$_2$), 51.3 (HN*C*H$_2$), 51.9 (*C*Me), 54.4 (HNCH$_2$*C*H), 57.7 (N*C*H$_2$Ph), 90.1 (N*C*HN), 116.9 (HC=*C*H$_2$), 126.9, 128.2, 128.8 (aromatic *C*H), 135.1 (H*C*=CH$_2$), 139.1 (aromatic *C*); *m/z* (CI$^+$) 243 (MH$^+$, 100%), 214 (34), 173 (27). HRMS found 243.1854. Calc. for $C_{16}H_{23}N_2$ (MH$^+$) 243.1856.

(1*RS*,4*SR*,5*RS*)-8-Benzyl-5-methyl-2-(4-tolylsulfonyl)-4-vinyl-2,8-diazabicyclo[3.3.0]octane 29. 4-Tolylsulfonyl chloride (2.00 g, 10.5 mmol) was added to a stirred solution of amine **28** (1.27 g, 5.6 mmol) in pyridine (8.5 mL, 105 mmol) at 0 °C. The reaction was slowly allowed to warm to room temperature and stirred for 16 h. The mixture was diluted with EtOAc (50 mL) then washed with H$_2$O (20 mL) and saturated aqueous CuSO$_4$ (3 × 20 mL). The aqueous washes were re-extracted with EtOAc (3 × 30 mL), and the combined organic extracts washed with brine (2 × 10 mL) then dried (MgSO$_4$) and concentrated. Purification by flash chromatography (SiO$_2$; EtOAc–petrol 1 : 9 → 2 : 8) afforded the sulfonamide **29** (1.81 g, 87%) as a pale yellow solid; (Found: C, 69.4; H, 7.1; N, 7.0. Calc. for $C_{23}H_{28}N_2O_2S$: C, 69.7; H, 7.1; N, 7.1%); ν_{max}/cm^{-1} (CHCl$_3$ cast) 2923, 2878 (CH), 1599 (C=C), 1448, 1348, 1157; δ_H (400 MHz; CDCl$_3$) 0.96 (3H, s, NCHCC*H*$_3$), 1.20 (1H, ddd, *J* 12.8, 6.4, 5.1, BnNCH$_2$C*H*H), 1.75–1.88 (2H, m, TsNCH$_2$C*H* and BnNCH$_2$CH*H*), 2.43 (3H, s, ArC*H*$_3$), 2.58–2.72 (2H, m, BnNC*H*$_2$), 3.23 (1H, t, *J* 12.0) and 3.66 (1H, dd, *J* 12.0, 7.1, TsNC*H*$_2$), 4.05 (2H, s, NC*H*$_2$Ph), 4.68 (1H, s, NC*H*N), 4.91 (1H, d, *J* 17.4) and 5.06 (1H, d, *J* 10.5, HC=C*H*$_2$), 5.57 (1H, ddd, *J* 17.4, 10.5, 7.1, *H*C=CH$_2$), 7.20–7.36 (7H, m, Ar*H*), 7.77 (2H, d, *J* 8.2, Ar*H* *o*- to SO$_2$); δ_C (100 MHz; CDCl$_3$) 21.6 (Ar*C*H$_3$), 24.8 (NCHC*C*H$_3$), 31.1 (BnNCH$_2$*C*H$_2$), 50.4 (BnN*C*H$_2$), 51.7 (TsNCH$_2$*C*H), 52.0 (TsN*C*H$_2$), 52.9 (NCH*C*Me), 55.6 (N*C*H$_2$Ph), 90.7 (N*C*HN), 118.0 (HC=*C*H$_2$), 126.7, 127.2, 128.1, 128.7, 129.7 (aromatic *C*H), 133.8 (H*C*=CH$_2$), 137.2, 139.2, 143.3 (aromatic *C*); *m/z* (CI$^+$) 425 ([M + C$_2$H$_5$]$^+$, 21%), 397 (MH$^+$, 100), 241 (16), 213 (21), 172 (16), 125 (52), 93 (44). HRMS found 397.1950. Calc. for $C_{23}H_{29}N_2O_2S$ (MH$^+$) 397.1941.

2-[(1*RS*,4*SR*,5*RS*)-8-Benzyl-5-methyl-2-(4-tolylsulfonyl)-2,8-diazabicyclo[3.3.0]oct-4-yl]ethanol 31. A solution of alkene **29** (1.75 g, 4.4 mmol) and tris(triphenylphosphine)rhodium(I) chloride (0.12 g, 0.13 mmol) in THF (40 mL) was degassed by pump-filling with argon. Pinacolborane (1.9 mL, 13.2 mmol) was added slowly and the mixture degassed again, then stirred for 20 h. The reaction was cooled to 0 °C and treated successively with H$_2$O (40 mL) and NaBO$_3$·4H$_2$O (2.42 g, 13.2 mmol), stirred at 0 °C for 15 min then allowed to warm to room temperature. After a further 5 h, the product was extracted with EtOAc (3 × 40 mL) and the combined organic extracts washed with H$_2$O (2 × 40 mL), brine (2 × 40 mL) and dried (MgSO$_4$). Concentration and purification by flash chromatography (SiO$_2$; EtOAc–petrol 1 : 4 → 3 : 2) afforded alcohol **31** (1.51 g, 86%) as a pale yellow oil; ν_{max}/cm^{-1} (CHCl$_3$ cast) 3449br (OH), 2930, 2876 (CH), 1334, 1155; δ_H (500 MHz; $CDCl_3$) 0.92 (3H, s, NCHCC*H*$_3$), 1.26–1.35 (3H, m, C*H*HCH$_2$OH, TsNCH$_2$C*H*, and BnNCH$_2$C*H*H), 1.51 (1H, m, CH*H*CH$_2$OH), 1.58 (1H, br s, O*H*), 1.75 (1H, dt, *J* 12.6, 7.7, BnNCH$_2$CH*H*), 2.40 (3H, s, ArC*H*$_3$), 2.59 (1H, ddd, *J* 9.0, 7.6, 6.5) and 2.67 (1H, ddd, *J* 9.0, 7.3, 4.3, BnNC*H*$_2$), 2.99 (1H, t, *J* 12.0, TsNC*H*H), 3.44–3.55 (2H, m, C*H*$_2$OH), 3.74 (1H, dd, *J* 12.0, 6.7, TsNCH*H*), 3.99 (1H, d, *J* 13.9) and 4.07 (1H, d, *J* 13.9, NC*H*$_2$Ph), 4.60 (1H, s, NC*H*N), 7.18–7.32 (7H, m, Ar*H*), 7.75 (2H, d, *J* 8.2, Ar*H* *o*- to SO_2); δ_C (125 MHz; $CDCl_3$) 21.5 (Ar*C*H$_3$) 24.5 (NCHC*C*H$_3$), 30.2 (*C*H$_2$CH$_2$OH), 30.7 (BnNCH$_2$*C*H$_2$), 45.2 (TsNCH$_2$*C*H), 50.4 (BnN*C*H$_2$), 52.7 (TsN*C*H$_2$), 52.8 (NCH*C*Me), 55.8 (N*C*H$_2$Ph), 61.7 (O*C*H$_2$), 90.7 (N*C*HN), 126.7, 127.2, 128.1, 128.8, 129.6 (aromatic *C*H), 137.5, 139.1, 143.2 (aromatic *C*); *m*/*z* (ESI$^+$) 453 (MK$^+$, 14%), 437 (MNa$^+$, 14), 415 (MH$^+$, 100). HRMS found 415.2050. Calc. for $C_{23}H_{31}N_2O_3S$ (MH$^+$) 415.2051.

Aqueous workup and flash chromatography (SiO_2; EtOAc–petrol 1 : 19 → 1 : 4) prior to addition of the perborate allowed isolation of the boronate **30** as a white solid; (Found: C, 66.3; H, 7.9; N, 5.3. Calc. for $C_{29}H_{41}BN_2O_4S$: C, 66.4; H, 7.9; N, 5.3%); δ_H (500 MHz; $CDCl_3$) 0.50 (1H, ddd, *J* 15.8, 10.3, 5.8) and 0.61 (1H, ddd, *J* 15.8, 11.0, 5.8, BC*H*$_2$), 0.89 (3H, s, NCHCC*H*$_3$), 1.02 (1H, m, TsNCH$_2$C*H*), 1.18 (6H, s) and 1.19 (6H, s, (C*H*$_3$)$_2$CC(C*H*$_3$)$_2$), 1.10–1.25 (2H, m, BCH$_2$C*H*$_2$), 1.33 (1H, m) and 1.76 (1H, dt, *J* 12.6, 7.5, BnNCH$_2$C*H*$_2$), 2.39 (3H, s, ArC*H*$_3$), 2.58 (1H, m) and 2.64 (1H, m, BnNC*H*$_2$), 2.92 (1H, t, *J* 12.0) and 3.68 (1H, dd, *J* 12.0, 6.9, TsNC*H*$_2$), 4.01 (1H, d, *J* 14.0) and 4.05 (1H, d, *J* 14.0, NC*H*$_2$Ph), 4.58 (1H, s, NC*H*N), 7.16–7.32 (7H, m, Ar*H*), 7.72 (2H, d, *J* 8.2, Ar*H* *o*- to SO_2); δ_C (125 MHz; $CDCl_3$) 10.2 (br, B*C*H$_2$), 21.3 (BCH$_2$*C*H$_2$), 21.5 (Ar*C*H$_3$), 24.7, 24.8 (NCHC*C*H$_3$ and (H$_3$*C*)$_2$CC(*C*H$_3$)$_2$), 30.5 (BnNCH$_2$*C*H$_2$), 50.4 (TsNCH$_2$*C*H), 50.5 (BnN*C*H$_2$), 52.5 (TsN*C*H$_2$), 52.8 (NCH*C*Me), 55.6 (N*C*H$_2$Ph), 83.1 ((H$_3$C)$_2$*CC*(CH$_3$)$_2$), 91.4 (N*C*HN), 126.6, 127.2, 128.8, 129.5 (aromatic *C*H), 137.4, 139.2, 143.0 (*C*); *m*/*z* (CI$^+$) 525 (MH$^+$, 69%), 371 (16), 171 (31), 125 (100), 93 (88). HRMS found 525.2945. Calc. for $C_{29}H_{42}BN_2O_4S$ (MH$^+$) 525.2958.

2-[(1*RS*,4*SR*,5*RS*)-8-Benzyl-5-methyl-2-(4-tolylsulfonyl)-2,8-diazabicyclo[3.3.0]oct-4-yl]ethanal 32. To a solution of alcohol **31** (1.48 g, 3.6 mmol) in CH_2Cl_2 (50 mL) at 0 °C were added pyridine (2.9 mL, 36 mmol) and 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1*H*)-one (3.8 g, 8.9 mmol). The reaction mixture was allowed to warm to room temperature, and after 16 h, was quenched by addition of saturated aqueous $Na_2S_2O_3$ (40 mL) and saturated aqueous $NaHCO_3$ (40 mL). After vigorously stirring for 1 h, the organic materials were extracted with CH_2Cl_2 (2 × 50 mL), washed with saturated aqueous $CuSO_4$ (3 × 40 mL), brine (40 mL) and then dried ($MgSO_4$) and concentrated. Purification by flash chromatography (SiO_2; EtOAc–petrol 3 : 7) afforded aldehyde **32** (1.18 g, 80%) as a pale yellow oil; ν_{max}/cm^{-1} ($CHCl_3$ cast) 2928, 2822 (CH), 1724 (C=O), 1599, 1454, 1334, 1155; δ_H (500 MHz; $CDCl_3$) 0.87 (3H, s, NCHCC*H*$_3$), 1.20 (1H, ddd, *J* 11.0, 6.5, 4.6, BnNCH$_2$C*H*H), 1.54–1.74 (2H, m, BnNCH$_2$CH*H* and TsNCH$_2$C*H*), 2.22 (1H, ddd, *J* 17.8, 10.1, 1.0) and 2.39 (1H, m, C*H*$_2$CHO), 2.41 (3H, s, ArC*H*$_3$), 2.60 (1H, m) and 2.68 (1H, m, BnNC*H*$_2$), 2.95 (1H, t, *J* 12.2) and 3.87 (1H, dd, *J* 12.2, 6.9, TsNC*H*$_2$), 4.00 (1H, d, *J* 13.9) and 4.08 (1H, d, *J* 13.9, NC*H*$_2$Ph), 4.57 (1H, s, NC*H*N), 7.19–7.33 (7H, m, Ar*H*), 7.78 (2H, d, *J* 8.3, Ar*H* *o*- to SO_2), 9.64 (C*H*O); δ_C (125 MHz; $CDCl_3$) 21.5 (Ar*C*H$_3$), 24.4 (NCHC*C*H$_3$), 30.9 (BnNCH$_2$*C*H$_2$), 41.5 (*C*H$_2$CHO), 41.9 (TsNCH$_2$*C*H), 50.1 (BnN*C*H$_2$), 52.2 (TsN*C*H$_2$), 52.4 (NCH*C*Me), 55.4 (N*C*H$_2$Ph), 90.1 (N*C*HN), 126.8, 127.3, 128.1, 128.8, 129.7 (aromatic *C*H), 137.1, 138.8, 143.4 (aromatic *C*), 199.9 (*C*=O); *m*/*z* (CI$^+$) 413 (MH$^+$, 100%), 257 (17), 229 (20), 157 (27), 91 (67). HRMS found 413.1895. Calc. for $C_{23}H_{29}N_2O_3S$ (MH$^+$) 413.1899.

2-[(1*RS*,4*SR*,5*RS*)-8-Benzyl-5-methyl-2-(4-tolylsulfonyl)-2,8-diazabicyclo[3.3.0]oct-4-yl]ethanoic acid 33. To a solution of aldehyde **32** (0.62 g, 1.5 mmol) in *t*-BuOH (10 mL) and H_2O (6 mL) at 0 °C was added 2-methyl-2-butene (1.9 mL, 18.1 mmol), followed by a solution of $NaClO_2$ (0.68 g, 7.6 mmol) and KH_2PO_4 (1.0 g, 7.6 mmol) in H_2O (14 mL). The mixture was stirred at 0 °C for 3 h then allowed to warm to room temperature. The reaction was quenched by the addition of aqueous $Na_2S_2O_3$ (5% w/v, 16 mL), and then the mixture acidified to pH 6.0 with 1% aqueous HCl. The organic material was extracted with EtOAc (3 × 20 mL), then the combined extracts dried ($MgSO_4$) and concentrated. The brown solid residue was dissolved in EtOAc (20 mL), then extracted with aqueous NaOH (0.1 M, 3 × 20 mL). The combined aqueous extracts were acidified to pH 6.0 with 1% aqueous HCl, then extracted with EtOAc (3 × 50 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated to afford the acid **33** (0.55 g, 85%) as a peach-coloured foamy solid; ν_{max}/cm^{-1} ($CHCl_3$ cast) 3412br (OH), 2928, 2878 (CH), 1719 (C=O), 1597, 1452, 1346, 1159; δ_H (500 MHz; $CDCl_3$) 0.84 (3H, s, NCHCC*H*$_3$), 1.20 (1H, ddd, *J* 12.5, 6.2, 4.0, BnNCH$_2$C*H*H), 1.56 (1H, m, TsNCH$_2$C*H*), 1.73 (1H, dt, *J* 12.5, 7.5, BnNCH$_2$CH*H*), 2.11 (1H, dd, *J* 16.4, 10.7) and 2.27 (1H, dd, *J* 16.4, 3.6, C*H*$_2$CO$_2$H), 2.39 (3H, s, ArC*H*$_3$), 2.62 (1H, m) and 2.75 (1H, ddd, *J* 9.1, 7.5, 4.0, BnNC*H*$_2$), 3.06 (1H, t, *J* 12.2) and 3.93 (1H, dd, *J* 12.2, 6.9, TsNC*H*$_2$), 4.03 (1H, d, *J* 13.8) and 4.09 (1H, d, *J* 13.8, NC*H*$_2$Ph), 4.58 (1H, s, NC*H*N), 7.19–7.35 (7H, m, Ar*H*), 7.68 (1H, br s, CO$_2$*H*), 7.76 (2H, d, *J* 8.2, Ar*H* *o*- to SO_2); δ_C (125 MHz; $CDCl_3$) 21.5 (Ar*C*H$_3$), 24.0 (NCHC*C*H$_3$), 30.6 (BnNCH$_2$*C*H$_2$), 32.7 (*C*H$_2$CO$_2$H), 43.7 (TsNCH$_2$*C*H), 50.1 (BnN*C*H$_2$), 52.2 (NCH*C*Me), 52.6 (TsN*C*H$_2$), 55.3 (N*C*H$_2$Ph), 89.9 (N*C*HN), 127.0, 127.3, 128.2, 129.2, 129.8 (aromatic *C*H), 136.9, 138.0, 143.5 (aromatic *C*), 177.0 (*C*=O); *m*/*z* (CI$^+$) 429 (MH$^+$, 100%), 273 (24), 186 (39). HRMS found 429.1841. Calc. for $C_{23}H_{29}N_2O_4S$ (MH$^+$) 429.1848.

(1*RS*,7*SR*)-4-Benzyl-8-hydroxy-7-methyl-9-(4-tolylsulfonyl)-4,9-diazabicyclo[5.3.0]decan-3-one 34. To a stirred solution of acid **33** (0.11 g, 0.25 mmol) in THF (2 mL) at −10 °C were added Et_3N (0.046 mL, 0.33 mmol) and isobutyl chloroformate (0.043 mL, 0.33 mmol). After 1 h, $TMSCHN_2$ (2 M in Et_2O, 0.25 mL, 0.50 mmol) was added, and after an additional 2 h, further $TMSCHN_2$ (2 M in Et_2O, 0.25 mL, 0.50 mmol) was added, and the mixture was allowed to warm to room temperature. After a further 16 h, the mixture was concentrated and purified by flash chromatography (SiO_2; EtOAc–petrol 1 : 4 → 3 : 2) to afford slightly impure lactam **34** (0.066 g, <62%) as a white solid; ν_{max}/cm^{-1} (KBr disc) 3350br (OH), 2927, 2881 (CH), 1630 (C=O), 1342, 1169; δ_H (500 MHz; $CDCl_3$) 0.83 (1H, dd, *J* 14.2, 11.5, BnNCH$_2$C*H*H), 1.04 (3H, s, CH(OH)CC*H*$_3$), 1.10 (1H, dd, *J* 14.2, 6.2, BnNCH$_2$CH*H*), 2.39 (1H, m, TsNCH$_2$C*H*), 2.44 (3H, s, ArC*H*$_3$), 2.50 (1H, dd, *J* 14.8, 7.2) and 2.77 (1H, d, *J* 14.8, O=CC*H*$_2$), 2.82 (1H, dd, *J* 15.6, 6.2, BnNC*H*H), 2.91 (1H, m, TsNC*H*H), 3.32 (1H, dd, *J* 15.6, 11.5, BnNCH*H*), 3.38 (1H, br s, O*H*), 3.60 (1H, m, TsNCH*H*), 3.77 (1H, d, *J*

14.7, NCHHPh), 4.80 (1H, s, NCH(OH)), 4.86 (1H, d, J 14.7, NCHHPh), 7.10–7.35 (7H, m, ArH), 7.74 (2H, d, J 8.1, ArH o- to SO_2); δ_C (125 MHz; $CDCl_3$) 18.5 (CH(OH)CCH_3), 21.6 (ArCH_3), 32.6 (BnN$CH_2$$CH_2$), 33.1 (O=C$CH_2$), 38.6 (TsN$CH_2$$C$H), 42.7 (BnN$CH_2$), 46.5 (TsNCH$C$Me), 49.0 (TsN$CH_2$), 50.4 (N$CH_2$Ph), 90.0 (N$C$H(OH)), 127.3, 127.6, 128.0, 128.7, 129.8 (aromatic CH), 135.5, 136.9, 143.7 (aromatic C), 172.1 (C=O); m/z (FAB$^+$) 429 (MH$^+$, 5%), 307 (44), 289 (14), 154 (100). HRMS found 429.1846. Calc. for $C_{23}H_{29}N_2O_4S$ (MH$^+$) 429.1848.

3-[(1*RS*,4*SR*,5*RS*)-8-Benzyl-5-methyl-2-(4-tolylsulfonyl)-2,8-diazabicyclo[3.3.0]oct-4-yl]propan-2-ol 35. To a stirred solution of aldehyde **32** (0.63 g, 1.5 mmol) in THF (18 mL) at 0 °C was added MeMgBr (1.0 M in THF, 3.1 mL, 3.1 mmol). The temperature was maintained at 0 °C for 15 min then the flask was stirred at room temperature for 3 h and quenched by addition of saturated aqueous NH_4Cl (20 mL). The product was extracted into EtOAc (3 × 20 mL), washed with brine (20 mL), and then dried ($MgSO_4$) and concentrated. Purification by flash chromatography (SiO_2; EtOAc–petrol 3 : 7 → 2 : 3) afforded a 3 : 2 mixture of diastereoisomeric alcohols **35** (0.51 g, 78%) as a pale yellow oil; ν_{max}/cm^{-1} (film) 3449br (OH), 2982, 2877 (CH), 1454, 1336, 1157; δ_H (500 MHz; $CDCl_3$) 0.89 (1.2H, s) and 0.91 (1.8H, s, NCHCCH_3), 1.04 (1.8H, d, J 6.2) and 1.08 (1.2H, d, J 6.2, CH(OH)CH_3), 1.10–1.20 (2H, m, BnNCH$_2$CHH and TsNCH$_2$CH), 1.20–1.38 (2H, m, CH_2CH(OH)), 1.65 (1H, br s, OH), 1.68–1.77 (1H, m, BnNCH$_2$CHH), 2.40 (3H, s, ArCH_3), 2.56–2.62 (1H, m) and 2.63–2.69 (1H, m, BnNCH_2), 2.96 (0.4H, t, J 12.1) and 3.00 (0.6H, t, J 12.1, TsNCHH), 3.56–3.60 (0.6H, m) and 3.61–3.67 (0.4H, m, CH(OH)), 3.76 (0.4H, dd, J 12.2, 6.7) and 3.79 (0.6H, dd, J 12.2, 6.7, TsNCHH), 3.98–4.09 (2H, m, NCH_2Ph), 4.59 (1H, s, NCHN), 7.18–7.32 (7H, m, ArH),7.75 (1.2H, d, J 8.3) and 7.76 (0.8 H, d, J 8.3, ArH o- to SO_2); δ_C (125 MHz; $CDCl_3$) 21.5 (ArCH_3), 23.9, 24.0 (CH(OH)CH_3), 24.3, 24.6 (NCHCCH_3), 30.7 (BnNCH$_2$$CH_2$), 36.3, 36.7 ($CH_2$CH(OH)), 43.8, 46.0 (TsNCH$_2$$C$H), 50.3, 50.4 (BnN$CH_2$), 52.5, 52.8 (NCH$C$Me), 52.7, 53.2 (TsN$CH_2$), 55.6 (N$CH_2$Ph), 66.2, 67.6 ($C$H(OH)), 90.3, 90.7 (N$C$HN), 126.7, 127.0, 127.2, 127.3, 128.1, 128.8, 129.6 (aromatic CH), 137.4, 137.5, 139.1, 143.1, 143.2 (aromatic C); m/z (ESI$^+$) 451 (MNa$^+$, 100%), 429 (83), 258 (56). HRMS found 451.2036. Calc. for $C_{24}H_{32}N_2O_3SNa$ (MNa$^+$) 451.2031.

3-[(1*RS*,4*SR*,5*RS*)-8-Benzyl-5-methyl-2-(4-tolylsulfonyl)-2,8-diazabicyclo[3.3.0]oct-4-yl]propan-2-one 36. To a stirred solution of alcohols **35** (0.46 g, 1.1 mmol) in CH_2Cl_2 (25 mL) at 0 °C were added pyridine (0.44 mL, 5.4 mmol) and 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1H)-one (1.1 g, 2.7 mmol). The reaction mixture was allowed to warm to room temperature, and after 5 h was quenched by addition of saturated aqueous $Na_2S_2O_3$ (25 mL) and saturated aqueous $NaHCO_3$ (25 mL). After vigorously stirring for 30 min, the organic materials were extracted with CH_2Cl_2 (3 × 30 mL), and the combined extracts were washed with brine (30 mL), dried ($MgSO_4$) and concentrated. Purification by flash chromatography (SiO_2; EtOAc–petrol 3 : 7 → 4 : 6) afforded methyl ketone **36** (0.36 g, 79%) as a pale yellow oil; ν_{max}/cm^{-1} ($CHCl_3$ cast) 2926, 2880 (CH), 1715 (C=O), 1599, 1448, 1348, 1159; δ_H (500 MHz; $CDCl_3$) 0.82 (3H, s, NCHCCH_3), 1.17 (1H, ddd, J 12.5, 6.5, 4.6, BnNCH$_2$CHH), 1.50 (1H, m, TsNCH$_2$CH), 1.66 (1H, dt, J 12.5, 7.5, BnNCH$_2$CHH), 2.03 (3H, s, COCH_3), 2.11 (1H, dd, J 17.6, 10.5) and 2.34 (1H, dd, J 17.6, 3.2, CH_2COMe), 2.39 (3H, s, ArCH_3), 2.58 (1H, m) and 2.65 (1H, ddd, J 9.0, 7.5, 4.6, BnNCH_2), 2.89 (1H, t, J 12.2) and 3.88 (1H, dd, J 12.2, 6.9, TsNCH_2), 4.00 (1H, d, J 13.8) and 4.08 (1H, d, J 13.8, NCH_2Ph), 4.50 (1H, s, NCHN), 7.18–7.35 (7H, m, ArH), 7.78 (2H, d, J 8.2, ArH o- to SO_2); δ_C (125 MHz; $CDCl_3$) 21.5 (ArCH_3), 24.4 (NCHCCH_3), 30.1 (O=CCH_3), 31.0 (BnNCH$_2$$CH_2$), 41.4 ($CH_2$COMe), 42.7 (TsNCH$_2$$C$H), 50.1 (BnN$CH_2$), 52.1 (NCH$C$Me), 52.6 (TsN$CH_2$), 55.3 (N$CH_2$Ph), 90.2 (N$C$HN), 126.7, 127.4, 128.1, 128.8, 129.7 (aromatic CH), 137.0, 139.0, 143.3 (aromatic C), 206.5 (C=O); m/z (ESI$^+$) 449 (MNa$^+$, 45%), 427 (MH$^+$, 100), 242 (39). HRMS found 427.2047. Calc. for $C_{24}H_{31}N_2O_3S$ (MH$^+$) 427.2055.

3-[(1*RS*,4*SR*,5*RS*)-8-Benzyl-5-methyl-2-(4-tolylsulfonyl)-2,8-diazabicyclo[3.3.0]oct-4-yl]-2-(*tert*-butyldimethylsilanyloxy)propanal 38. To a solution of aldehyde **32** (0.32 g, 0.78 mmol) and TBSCN (0.22 g, 1.6 mmol) in CH_2Cl_2 (0.5 mL) was added LiCl (0.3 M solution in CH_2Cl_2, prepared by sonication for 15 min, 26 μL, 7.8 μmol) and the mixture was stirred for 2 d. The mixture was diluted with H_2O (5 mL) and the organic materials were extracted with EtOAc (3 × 5 mL), washed with brine (5 mL), dried ($MgSO_4$) and concentrated. Purification by flash chromatography (SiO_2; EtOAc–petrol 1 : 19 → 3 : 17) afforded a 3 : 2 diastereomeric mixture of protected cyanohydrins (0.37 g, 88%) as a pale yellow oil; ν_{max}/cm^{-1} ($CHCl_3$ cast) 2933 (CH), 2332 (C≡N), 1599, 1458, 1348, 1159; δ_H (500 MHz, $CDCl_3$) 0.10, 0.15 and 0.18 (6H, 3 × s, Si(CH_3)$_2$), 0.85, 0.90 and 0.91 (12H, 3 × s, NCHCCH_3 and C(CH_3)$_3$), 1.14–1.23 (1H, m, BnNCH$_2$CHH), 1.32–1.42 (1H, m, TsNCH$_2$CH), 1.49–1.62 (1H, m, CHHCHOTBS), 1.63–1.75 (2H, m, BnNCH$_2$CHH and CHHCHOTBS), 2.39 (3H, s, ArCH_3), 2.55–2.62 (1H, m) and 2.64–2.71 (1H, m, BnNCH_2), 3.01 (0.4H, t, J 12.2), 3.04 (0.6H, t, J 12.2) and 3.85–3.93 (1H, m, TsNCH_2), 3.98–4.04 (1H, m), 4.08 (0.6H, d, J 14.0) and 4.09 (0.4H, d, J 14.0, NCH_2Ph), 4.28 (0.6H, t, J 6.0) and 4.44 (0.4H, t, J 4.3, CHOTBS), 4.56 (0.6H, s) and 4.57 (0.4H, s, NCHN), 7.19–7.34 (7H, m, ArH), 7.72–7.77 (2H, m, ArH o- to SO_2); δ_C (125 MHz; $CDCl_3$) −5.5, −5.3, −5.2 (Si(CH_3)$_2$), 17.9, 18.0 (CMe$_3$), 21.5 (ArCH_3), 24.4 (NCHCCH_3), 25.5 (C(CH_3)$_3$), 30.9 (BnNCH$_2$$CH_2$), 34.1, 34.7 ($CH_2$CHOTBS), 43.8, 44.2 (TsNCH$_2$$C$H), 50.1 (BnN$CH_2$), 52.8, 53.0 (NCH$C$Me), 52.7, 53.5 (TsN$CH_2$), 55.4, 55.5 (N$CH_2$Ph), 61.0, 61.5 ($C$HOTBS), 89.9 (N$C$HN), 119.0, 119.4 ($C$≡N), 126.7, 126.8, 127.1, 127.2, 128.1, 128.8, 129.9 (aromatic CH), 136.9, 137.1, 139.0, 143.4, 143.6 (aromatic C); m/z (FAB$^+$) 576 (MNa$^+$, 93%), 554 (MH$^+$, 78), 381 (100), 176 (58). HRMS found 576.2702. Calc. for $C_{30}H_{43}N_3O_3SSiNa$ (MNa$^+$) 576.2692.

To a solution of the silylated cyanohydrin (0.28 g, 0.51 mmol) in toluene (5 mL) at −78 °C was added DIBAL (20 wt% in toluene, 0.68 mL, 0.82 mmol) dropwise. After stirring for 1.5 h at −78 °C, aqueous sodium potassium tartrate (0.5 M, 5 mL) was added and the stirring mixture was allowed to warm to room temperature. After 30 min, the organic materials were extracted with EtOAc (3 × 5 mL), washed with brine (5 mL), dried ($MgSO_4$) and concentrated. Purification by flash chromatography (SiO_2; EtOAc–petrol 1 : 19 → 1 : 9) afforded a 3 : 2 diastereomeric mixture of aldehydes **38** (0.12 g, 42%) as a pale yellow oil; ν_{max}/cm^{-1} ($CHCl_3$ cast) 2934 (CH), 1702 (C=O), 1597, 1460, 1339, 1159; δ_H (500 MHz, $CDCl_3$) 0.03 (3.6H, s) and 0.07 (2.4H, s, Si(CH_3)$_2$), 0.87, 0.89, 0.91 (12H, 3 × s, NCHCCH_3 and C(CH_3)$_3$), 1.09–

1.21 (1.4H, m, $TsNCH_2CH_{minor}$ and $BnNCH_2CHH$), 1.35–1.76 (3.6H, m, $BnNCH_2CHH$, $CH_2CHOTBS$ and $TsNCH_2CH_{major}$), 2.41 (3H, s, $ArCH_3$), 2.54–2.61 (1H, m) and 2.64–2.71 (1H, m, $BnNCH_2$), 2.96 (0.4H, t, *J* 12.0) and 2.97 (0.6H, t, *J* 12.0, TsNC*H*H), 3.67 (0.6H, dd, *J* 12.2, 6.9, $TsNCHH_{major}$), 3.79–3.87 (0.8H, m, CH_{minor}OTBS and $TsNCHH_{minor}$), 3.89–3.92 (0.6H, m, CH_{major}OTBS), 3.96 (0.4H, d, *J* 13.5), and 3.98 (0.6H, d, *J* 13.5, NC*H*HPh) 4.07 (0.6H, d, *J* 13.5) and 4.10 (0.4H, d, *J* 13.5, NCH*H*Ph), 4.56 (0.4H, s) and 4.58 (0.6H, s, NC*H*N) 7.17–7.34 (7H, m, Ar*H*), 7.71 (1.2H, d, *J* 8.3) and 7.72 (0.8H, d, *J* 8.3, Ar*H* *o*- to SO_2), 9.41 (0.6H, s) and 9.46 (0.4H, d, *J* 1.8, C*H*O); δ_C (125 MHz; $CDCl_3$) −5.0, −4.9, −4.7, −4.6 ($Si(CH_3)_2$), 18.0, 18.1 (CMe_3), 21.5 ($ArCH_3$), 24.2, 24.3 ($NCHCCH_3$), 25.7 ($C(CH_3)_3$), 30.5, 30.7, 30.9 ($CH_2CHOTBS$ and $BnNCH_2CH_2$), 43.5, 43.8 ($TsNCH_2CH$), 50.1, 50.3 ($BnNCH_2$), 52.9, 53.0 (NCH*C*Me), 53.1, 53.4 ($TsNCH_2$), 55.7 (NCH_2Ph), 76.5, 76.6 (*C*HOTBS), 89.9, 90.0 (N*C*HN), 126.7, 127.0, 127.1, 127.2, 128.1, 128.8, 129.8, 129.9 (aromatic *C*H), 137.3, 137.5, 139.0, 143.1, 143.2 (aromatic *C*), 204.6, 205.5 (*C*HO); *m/z* (FAB^+) 557 (MH^+, 34%), 286 (23), 173 (100), 154 (93). HRMS found 557.2883. Calc. for $C_{30}H_{45}N_2O_4SSi$ (MH^+) 557.2870.

(1*RS*,2*RS*,6*RS*,7*RS*,10*RS*)-3-Benzyl-1-(*tert*-butyldimethylsilanyloxy)-6-methyl-9-(4-tolylsulfonyl)-3,9-diazatricyclo[5.3.1.0^{2,6}]-undecan-10-ol 42. To a solution of aldehydes **38** (0.03 g, 0.05 mmol) in MeOH (0.5 mL) was added AcOH (0.012 mL, 0.22 mmol) and the mixture was stirred at room temperature for 16 h, then at 65 °C for a further 30 h. After cooling to room temperature, the mixture was concentrated, diluted with EtOAc (5 mL) and washed with saturated aqueous $NaHCO_3$ (5 mL). The organic materials were extracted from the aqueous layer with EtOAc (2 × 5 mL), and the combined organic extracts washed with brine (5 mL), dried ($MgSO_4$) and concentrated. Purification by flash chromatography (SiO_2; EtOAc–petrol 1 : 9 → 1 : 4) afforded slightly impure tricycle **42** (0.017 g, *ca.* 47%) as a pale yellow oil; ν_{max}/cm^{-1} ($CHCl_3$ cast) 3412 (OH), 2926 (CH), 1599, 1456, 1336, 1159 (SO_2); δ_H (500 MHz; $CDCl_3$) 0.11 (3H, s) and 0.15 (3H, s, $Si(CH_3)_2$), 0.86 (9H, s, $C(CH_3)_3$), 0.88 (3H, s, $NCHCCH_3$), 1.46 (1H, dd, *J* 12.5, 5.8, $BnNCH_2CHH$), 1.50–1.75 (4H, m, $BnNCH_2CHH$, $TsNCH_2CH$, C*H*HCOTBS and O*H*), 2.11 (1H, d, *J* 11.8, CH*H*COTBS), 2.33 (1H, s, BnNC*H*CMe), 2.42 ($ArCH_3$), 2.43 (1H, m) and 2.90 (1H, dd, *J* 9.0, 7.3, $BnNCH_2$), 3.03 (1H, dd, *J* 11.3, 1.5) and 3.21 (1H, m, $TsNCH_2$), 3.47 (1H, d, *J* 13.1) and 4.04 (1H, d, *J* 13.1, NCH_2Ph), 5.30 (1H, s, NC*H*OH), 7.20–7.37 (7H, m, Ar*H*), 7.79 (2H, d, *J* 8.3, Ar*H* *o*- to SO_2); δ_C (125 MHz; $CDCl_3$) −4.3, −3.9 ($Si(CH_3)_2$), 18.5 (CMe_3), 21.4 ($NCHCCH_3$), 21.5 ($ArCH_3$), 26.1 ($C(CH_3)_3$), 33.7 (CH_2COTBS), 39.4 ($BnNCH_2CH_2$), 41.1 ($TsNCH_2CH$), 44.0 ($TsNCH_2$), 49.3 (NCH*C*Me), 52.8 ($BnNCH_2$), 62.3 (NCH_2Ph), 76.4 (BnN*C*HCMe), 79.3 (*C*OTBS), 84.2 (*C*HOH), 127.2, 127.9, 128.4, 128.6, 129.4 (aromatic *C*H), 136.7, 139.0, 143.3 (aromatic *C*), *m/z* (EI^+) 556 (M^+, 2%), 499 (67), 269 (86), 95 (100). HRMS found 556.2781. Calc. for $C_{30}H_{44}N_2O_4SSi$ (M^+) 556.2786.

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