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Stereoselective synthesis of oxazolidinonyl-fused piperidines of interest as selective muscarinic (M_1) receptor agonists: a novel M_1 allosteric modulator‡

Kenneth J. Broadley,[a] Maxime G. P. Buffat,[b] Erica Burnell,[b] Robin H. Davies,†[c] Xavier Moreau,[b] Stephen Snee[b] and Eric J. Thomas*[b]

Syntheses of (1*RS*,2*SR*,6*SR*)-2-alkoxymethyl-, 2-hetaryl-, and 2-(hetarylmethyl)-7-arylmethyl-4,7-diaza-9-oxabicyclo[4.3.0]nonan-8-ones, of interest as potential muscarinic M_1 receptor agonists, are described. A key step in the synthesis of (1*RS*,2*SR*,6*SR*)-7-benzyl-6-cyclobutyl-2-methoxymethyl-4,7-diaza-9-oxabicyclo[4.3.0]nonan-8-one, was the addition of isopropenylmagnesium bromide to 2-benzyloxycarbonylamino-3-*tert*-butyldimethylsilyloxy-2-cyclobutylpropanal. This gave the 4-*tert*-butyldimethylsilyloxymethyl-4-cyclobutyl-5-isopropenyloxazolidinone with the 5-isopropenyl and 4-*tert*-butyldimethylsilyloxymethyl groups *cis*-disposed about the five-membered ring by chelation controlled addition and *in situ* cyclisation. This reaction was useful for a range of organometallic reagents. The hydroboration–oxidation of (4*SR*,5*RS*)-3-benzyl-4-(*tert*-butyldimethylsilyloxymethyl)-4-cyclobutyl-5-(1-methoxyprop-2-en-2-yl)-1,3-oxazolidin-2-one gave (4*SR*,5*RS*)-3-benzyl-4-(*tert*-butyldimethylsilyloxymethyl)-4-cyclobutyl-5-[(*SR*)-1-hydroxy-3-methoxyprop-2-yl]-1,3-oxazolidin-2-one stereoselectively. 4,7-Diaza-9-oxabicyclo[4.3.0]nonan-8-ones with substituents at C2 that could facilitate C2 deprotonation were unstable with respect to oxazolidinone ring-opening and this restricted both the synthetic approach and choice of 2-heteroaryl substituent. The bicyclic system with a 2-furyl substituent at C2 was therefore identified as an important target. The addition of 1-lithio-1-(2-furyl)ethene to 2-benzyloxycarbonylamino-3-*tert*-butyldimethylsilyloxy-2-cyclobutylpropanal gave (4*SR*,5*RS*)-4-*tert*-butyldimethylsilyloxymethyl-4-cyclobutyl-5-[1-(2-furyl)ethenyl]-1,3-oxazolidinone after chelation controlled addition and *in situ* cyclisation. Following oxazolidinone *N*-benzylation, hydroboration at 35 °C, since hydroboration at 0 °C was unexpectedly selective for the undesired isomer, followed by oxidation gave a mixture of side-chain epimeric alcohols that were separated after SEM-protection and selective desilylation. Conversion of the neopentylic alcohols into the corresponding primary amines by reductive amination, was followed by *N*-nosylation, removal of the SEM-groups and cyclisation using a Mitsunobu reaction. Denosylation then gave the 2-furyloxazolidinonyl-fused piperidines, the (1*RS*,2*SR*,6*SR*)-epimer showing an allosteric agonistic effect on M_1 receptors. Further studies resulted in the synthesis of other 2-substituted 4,7-diaza-9-oxabicyclo[4.3.0]nonan-8-ones and an analogous tetrahydropyran.

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Introduction

Muscarinic acetylcholine receptors are a group of widely distributed G-protein coupled receptors that are involved in many metabolic processes.[1] In particular, the M_1 muscarinic acetylcholine receptors have a critical role in cognitive processing.[2] In patients with Alzheimer's disease, decreased cholinergic activity is associated with reduced acetylcholine mediated neurotransmission in regions expressing M_1 receptors, although the receptors themselves appear to be unchanged. Agonists of muscarinic M_1 receptors are therefore targets as chemotherapeutic agents for Alzheimer's disease. Several

[a]*Cardiff School of Pharmacy and Pharmaceutical Sciences, Cardiff University, Redwood Building, King Edward VII Avenue, Cardiff, CF10 3NB, UK*
[b]*The School of Chemistry, The University of Manchester, Manchester, M13 9PL, UK. E-mail: e.j.thomas@manchester.ac.uk*
[c]*Muscagen Limited, 10, North Road, Cardiff, CF10 3DY, UK*
†Deceased October 2012.

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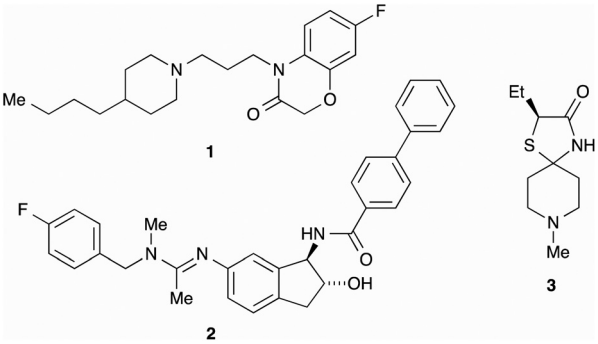


Fig. 1 Representative muscarinic M_1 receptor agonists.

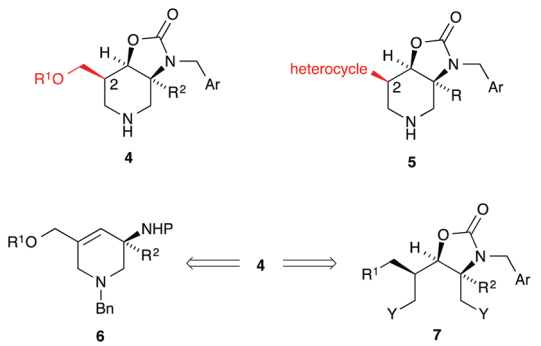


Fig. 2 Synthetic targets and possible routes.

muscarinic M_1 receptor agonists have been discovered, *e.g.* **1–3**, see Fig. 1, including some that function *via* an allosteric mechanism,[3,4] and some agonists have been shown to alleviate the symptoms of Alzheimer's disease.[5,6] Nevertheless, there remains a need for more compounds that show selective agonist activity against M_1 receptors to avoid side-effects arising from stimulation of other muscarinic receptor subtypes.

Molecular modelling studies using the bacterial rhodopsin as a substitute for the M_1 receptor, led to the identification of the oxazolidinonyl fused piperidines **4** and **5**, characterised by different substituents at C2, see Fig. 2, as possible M_1 agonists with improved selectivity.[7] However to test this hypothesis it was necessary to synthesise representative members of the series so that they could be evaluated biologically. The first approach to the 2-(alkoxymethyl)piperidines **4** that was investigated involved the regio- and stereo-selective hydration of 1,2,5,6-tetrahydropyridines, *e.g.* **6**, followed by oxazolidinone formation. However, preliminary studies of the synthesis and functionalisation of 1,2,5,6-tetrahydropyridines **6** en route to the oxazolidinonylpiperidines **4** met with unexpected complications[8] and was discontinued in favour of a second strategy in which the piperidine ring was assembled on an oxazolidinone, *e.g.* **7**. This approach led to the successful synthesis of the first member of the series, the piperidine **4** (R^1 = Me; R^2 = cyclobutyl; Ar = Ph).[9] Full details of this synthesis and the extension of this approach to complete syntheses of several piperidines **4** and **5** are presented herein together with the results of preliminary biological investigations.[9]

Results and discussion

Synthesis of 2-(alkoxymethyl)piperidines 4 from oxazolidinones 7

The oxazolidinonyl-fused piperidine **8** with a methoxymethyl group at C2 and a cyclobutyl substituent at C6 was selected as the first target for synthesis, the size of the cyclobutyl substituent being optimal. The oxazolidinone **9** was identified as a likely precursor of the piperidine **8** providing the configurations of its three stereogenic centres could be controlled, with the aldehyde **10** a possible intermediate for the synthesis of oxazolidinone **9**, see Fig. 3. The cyclobutyl group in the aldehyde **10** limited the options that were available for its synthesis. It was decided to study the synthesis of this aldehyde from the ketone **11** which in turn would be prepared from the commercially available cyclobutane carboxylic acid (**12**).

The (*tert*-butyldimethylsilyloxy)methyl ketone **11** was prepared from cyclobutane carboxylic acid (**12**) by reaction with methyllithium, bromination, hydrolysis of the bromide and silylation. A Wadsworth–Emmons–Horner reaction of ketone **11** then gave the unsaturated ester **16** that was reduced to give the allylic alcohol **17**, $(Z):(E)$ = 75 : 25, see Scheme 1. The (Z)-geometry of the major product (Z)-**17** was established by nOe between H2 and 3-CH.

[3,3]-Sigmatropic rearrangements were investigated for the conversion of the alcohol **17** into the aldehyde **10**.[11–13] The allylic alcohols **17** were first converted into the trifluoroacetimidates **18** that were heated under reflux in xylene to give the tertiary trifluoroacetamide **19**. The trifluoroacetamide was then reduced using sodium borohydride to give the amine **20** that was protected as its Cbz-derivative **21**, see Scheme 2. This intermediate was also prepared, more conveniently, by [3,3]-sigmatropic rearrangement of the allylic cyanate derived from the alcohols **17** by reaction with trichloroacetyl isocyanate with *in situ* methanolysis of the adduct **22** to give the carbamate **23**.

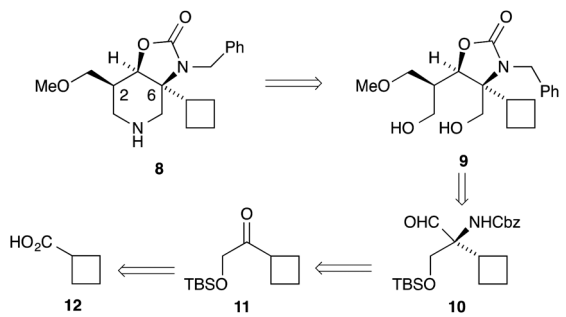
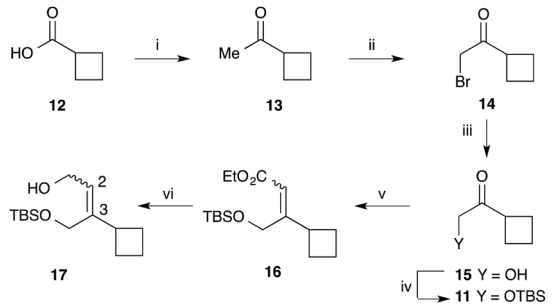
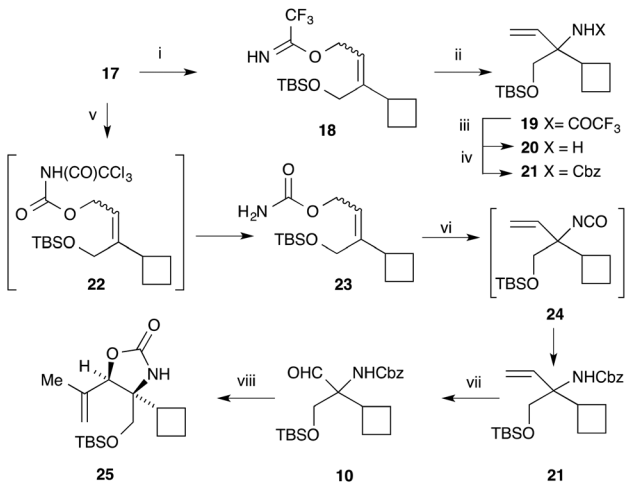


Fig. 3 Outline of the proposed synthesis of the oxazololidinonyl-fused piperidine **8**.



Scheme 1 Synthesis of the alkenol **17**. Reagents and conditions (i) MeLi, Et_2O, 0 °C to rt, 3 h (90%); (ii) Br_2, MeOH, 0 °C to 15 °C, 1.5 h (80%); (iii) KOCHO, MeOH, heat under reflux, 12 h (71%); (iv) TBSCl, imid., DMAP (cat.), TBAI (cat.), DCM, rt, 1 h (62%); (v) $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF, rt, 45 min, add **11**, rt, 2.5 h; (vi) DIBAL-H, hexanes, THF, −78 °C, 3 h, rt, 30 min [89% from **11**; (*Z*)-**17** : (*E*)-**17** = 75 : 25].



Scheme 2 Stereoselective synthesis of the racemic oxazolidinone **25**. Reagents and conditions (i) NaH, THF, rt, 1 h, add to CF_3CN, THF, −115 to −78 °C, 1 h (88%); (ii) xylene, heat under reflux 18 h (91%); (iii) $NaBH_4$, EtOH, 0 °C to rt, 18 h (80%); (iv) CbzCl, Et_3N, DCM, rt, 18 h (83%); (v) (a) $CCl_3C(O)NCO$, DCM, 0 °C, 1 h (b) MeOH, H_2O, K_2CO_3, 0 °C to rt, 3 h (70%); (vi) (a) Ph_3P, CBr_4, DCM, −10 °C, 1 h (b) BnONa, THF, rt, 1 h (83%). (vii) O_3, DCM, −78 °C, then Ph_3P, rt (84%); (viii) $CH_3C(MgBr)=CH_2$, THF, tol., −78 °C, 2 h, then rt, 48 h (66%).

This was dehydrated to generate the cyanate that underwent a spontaneous rearrangement to give the isomeric isocyanate **24** that in turn reacted with benzyl alcohol to give the Cbz-protected amine **21**, see Scheme 2.[13]

The aldehyde **10** was prepared from the alkene **21** by ozonolysis and the reaction of aldehyde **10** with isopropenylmagnesium bromide. This gave the oxazolidinone **25** that has the isopropenyl and *tert*-butyldimethylsilyloxymethyl groups *cis*-disposed about the five-membered ring, see Scheme 2. The configuration shown for the oxazolidinone **25** was established by X-ray diffraction,[9] and is consistent with the addition of the Grignard reagent taking place on the less hindered face of the *N*-deprotonated, chelated aldehyde **26** away from the cyclobutyl

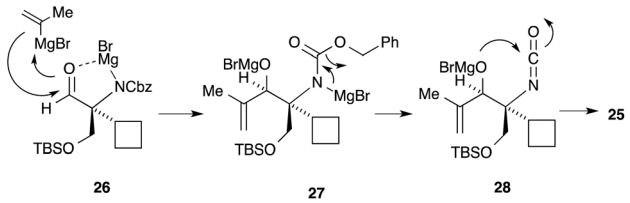


Fig. 4 Suggested mechanism for formation of oxazolidinone **25**.

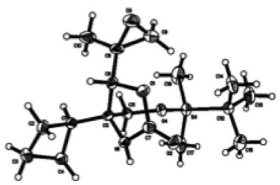
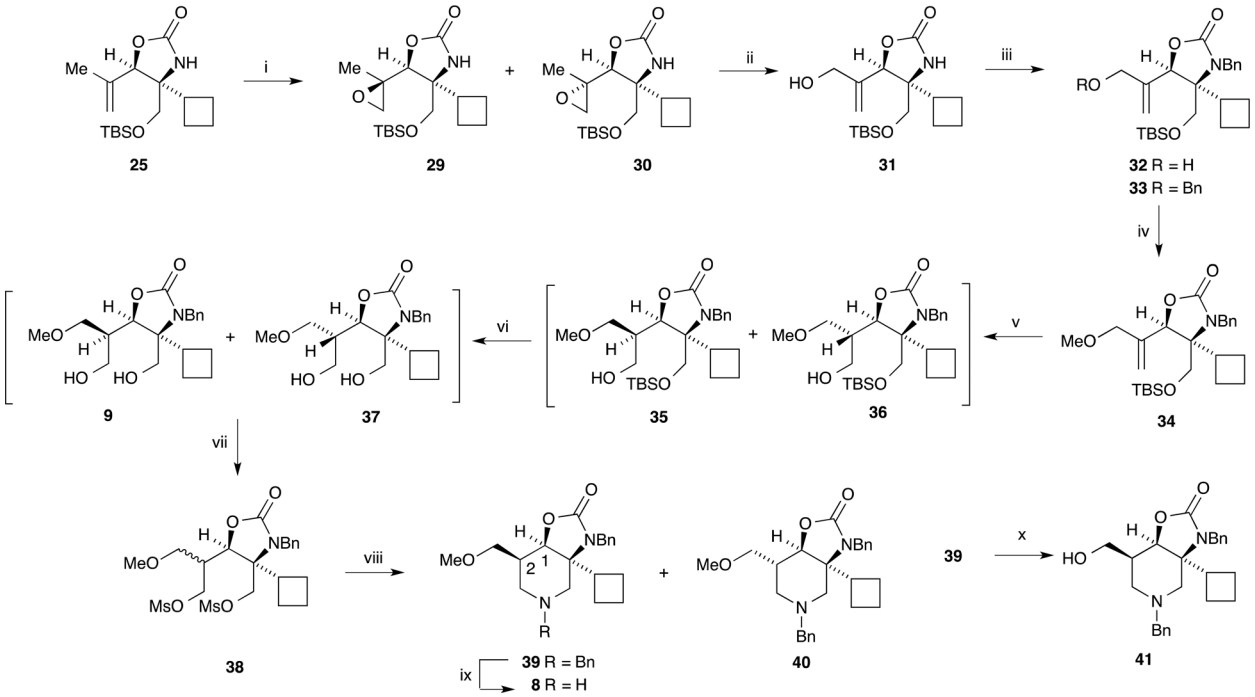


Fig. 5 The structure of epoxide **29** as established by X-ray diffraction.

group. This addition would give the adduct **27** that on standing was converted into the oxazolidinone **25** perhaps *via* the isocyanate **28** formed by loss of bromomagnesium benzyloxide from the adduct **27**, see Fig. 4.

To convert the oxazolidinone **25** into the cyclisation precursor **9** it was necessary to oxidise the methyl group and to hydrate the double bond stereoselectively. Epoxidation using *m*-chloroperoxybenzoic acid gave a mixture of the epoxides **29** and **30**, ratio 77 : 23. These epoxides could not easily be separated by chromatography, indeed this was not required for the synthesis, but the major isomer could be crystallised out of the mixture and was shown to be the epimer **29** by X-ray diffraction, see Fig. 5. The mixture of epoxides was reacted with lithium 2,2,6,6-tetramethylpiperidide to effect ring-opening to give the allylic alcohol **31**.[14] *N*-Benzylation then gave the *N*-benzyloxazolidinone **32** with just minor amounts, *ca.* 5%, of the benzyl ether **33**, and the alcohol **32** was converted into its methyl ether **34** using methyl iodide and sodium hydride, see Scheme 3.

The next step was to hydrate the double-bond of the methyl ether **34**. This was achieved by hydroboration using borane in tetrahydrofuran at 0 °C followed by oxidation. A mixture of the alcohols **35** and **36**, ratio 85 : 15, was obtained. This mixture could not be separated but the major product was confirmed as the required isomer **35** later in the synthesis. It would appear that the hydroboration of the double-bond had taken place selectively on the desired face of the double-bond perhaps *via* transition structure **42**, see Fig. 6. The mixture of alcohols **35** and **36** was desilylated to give a mixture of the diols **9** and **37** (ratio still *ca.* 85 : 15) and this mixture was cyclised by reaction of the corresponding bis-mesylates **38** with benzylamine. This gave a mixture of the epimeric piperidines **39** and **40** from which the major epimer **39** was isolated by chromatography and hydrogenolysis of the *N*-benzylpiperidine **39** gave the required *N*H-piperidine **8**, see Scheme 3.



Scheme 3 Synthesis of the oxazolidinonylpiperidine **8**. Reagents and conditions (i) *m*CPBA, DCM, rt, 18 h (75%, **29** : **30** = 77 : 23); (ii) 2,2,6,6-tetramethylpiperidine, THF, ^{n}BuLi, 0 °C to rt, 1 h, added to a mixture of **29** and **30**, THF, 0 °C to rt, 3 h (67%); (iii) NaH, BnBr, THF, heat under reflux, 6 h (**32**, 64%; **33**, 5%); (iv) NaH, THF, MeI, rt, 18 h (90%); (v) BH_3, THF, 0 °C, 18 h, then EtOH, NaOAc, 30% aq. H_2O_2, heat under reflux 1 h (95%, **35** : **36** = 85 : 15); (vi) TBAF, THF, 0 °C to rt , 30 min (67%, **9** : **37** = 85 : 15); (vii) MsCl , Et_3N, DCM , 0 °C to rt, 1 h; (viii) $BnNH_2$, 80 °C, 18 h (**39**, 36%; mixture of **39** and **40**, 26%, **39** : **40** = 56 : 44); (ix) 10% Pd/C, HCO_2H, MeOH, rt, 20 min (71%); (x) BBr_3, DCM, THF, 0 °C, 4 h (61%).

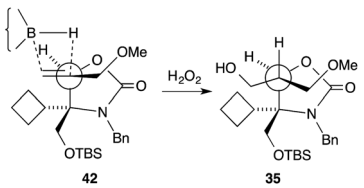


Fig. 6 Hydroboration of alkene **34**.

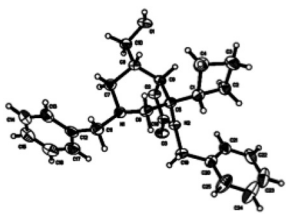
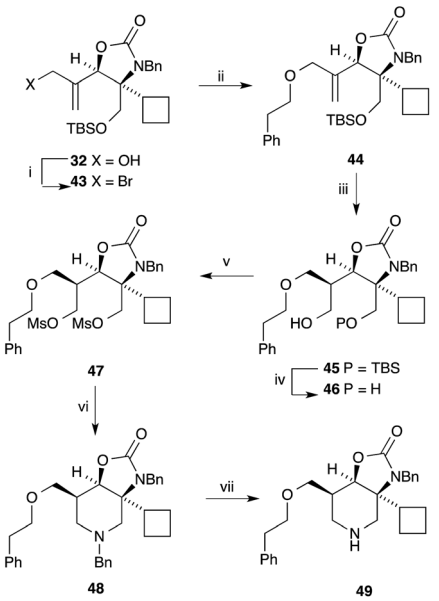


Fig. 7 The structure of the alcohol **41** as established by X-ray crystallography.

Structures were assigned to the products in Scheme 3 using spectroscopic data. The configurations of the piperidines **8**, **39** and **40** at C2 were difficult to assign by ^{1}H NMR although the vicinal coupling constant, $J_{1,2}$, was characteristic being smaller, typically less than 5 Hz for the required epimers **8** and **39**, and greater than 8 Hz for unwanted epimers, *e.g.* **40**. The structures of the piperidines and consequently of the hydroboration products **35** and **36** and intermediates **9**, **37** and **38** were eventually confirmed by an X-ray crystal structure determination of the alcohol **41** prepared by demethylation of the major *N*-benzyl(methoxymethyl)piperidine **39** using boron tribromide,[15] see Fig. 7.

The oxazolidinone-fused piperidine **8** was the first member of the series that had been identified as potential muscarinic M_1 receptor agonists to be synthesised and preliminary biological studies showed that it was a 50% partial agonist of the M_1 receptor with micromolar potency. The synthesis of other members of the series was therefore investigated.

The allylic bromide **43** was prepared from the alcohol **32** and was converted into the 2-phenylethyl ether **44** by treatment with the sodium alkoxide of 2-phenylethanol. Hydroboration/oxidation in this case gave a 3 : 1 mixture of epimers, the major epimer being identified as the required isomer **45** by analogy with the earlier work, see Scheme 4. Moreover, following desilylation, the structure of the crystalline diol **46** was confirmed by X-ray crystallography, see Fig. 8. The diol **46** was converted into the piperidine **48** *via* the bis-mesylate **47** as before and transfer hydrogenolysis gave the oxazolidinonylpiperidine **49**. The configurations of the piperidines **48** and **49** at C2 were consistent with their $J_{1,2}$ coupling constants of 2.5 Hz,



Scheme 4 Synthesis of the 2-(phenylethoxymethyl)piperidine **49**. Reagents and conditions (i) Ph_3P, CBr_4, MeCN, 0 °C, rt, 2 h (*ca.* 100%); (ii) $PhCH_2CH_2OH$, NaH, rt, 30 min, add **43**, rt, 3 h (99%); (iii) BH_3.THF, −20 °C to 0 °C, 18 h, add EtOH, NaOAc, 30% aq. H_2O_2, reflux, 2.5 h (47%); (iv) TBAF, THF, 0 °C to rt, 30 min (70%); (v) MsCl, Et_3N, 0 °C to rt, 1 h; (vi) $BnNH_2$, 95 °C, 15 h (37% from **46**); (vii) HCO_2H, Pd/C, MeOH, rt (61%).

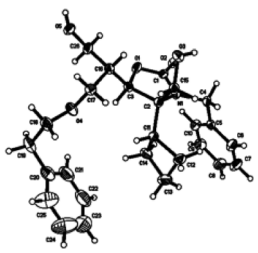
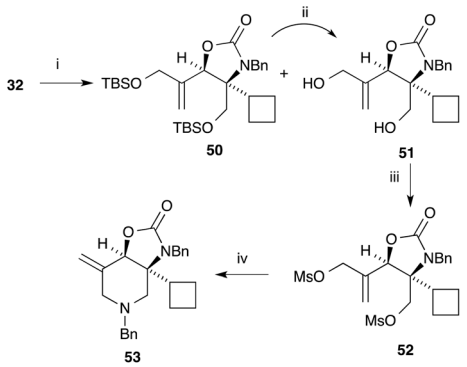


Fig. 8 The structure of the diol **46** as established by X-ray diffraction.

cf. the oxazolidinonylpiperidines **39** and **40**, and with the X-ray crystal structure of diol **46**.

An alternative synthesis of the ether **44** was investigated based on alkylation of the monosilylated diol **32**. However, during attempts to alkylate this alcohol using 2-phenylethyl bromide and sodium hydride, none of the expected ether **44** was obtained. Instead intermolecular silyl migration competed and a mixture of the bis-silyl ether **50** and the diol **51** was obtained. Desilylation of the bis-silyl ether gave more of the diol **51** that was cyclised to the piperidine **53** *via* its mesylate **52**. The chemistry of the piperidine **53** was not taken further, but the exocyclic double-bond would appear to provide a handle for further modification if so desired, see Scheme 5.

Having established a synthesis of the oxazolidinone-fused piperidines **4** with alkoxymethyl substituents at C2 as illustrated by the synthesis of piperidines **8** and **49**, the synthesis



Scheme 5 Synthesis of the 2-methylenepiperidine **53**. Reagents and conditions (i) NaH THF, rt, 30 min, $PhCH_2CH_2Br$, rt, 15 h (**50**, 38%; **51**, 43%); (ii) TBAF, THF, rt (54%); (iii) MsCl, Et_3N, DCM, 0 °C to rt, 1 h; (iv) $BnNH_2$, 95 °C, 18 h (**53**, 60%).

of the analogues **5** with hetaryl substituents at C2 was investigated since it was thought that the hetaryl group would improve selectivity for the M_1 receptor.[7]

Preliminary studies into the synthesis of 2-hetarylpiperidines 5

The 4-methyl-1,3-oxazole **54** was selected as the initial 2-hetarylpiperidine for synthesis,[7] see Fig. 9.

At this point, the oxidation of the alcohol **41** was investigated since the corresponding aldehyde and acid were perceived as useful late-stage intermediates for the introduction of various hetaryl groups at C2. However, oxidation of alcohol **41** using Swern conditions gave a good yield of the unsaturated aldehyde **56** rather than the required aldehyde **55**, see Scheme 6. It would appear that the aldehyde **55** is unstable under mildly basic conditions with respect to ring-opening of the oxazolidinone with loss of carbon dioxide. Attempted oxidation of alcohol **41** using the Dess–Martin periodinane gave a complex mixture of products.

The introduction of the oxazole ring earlier in the synthesis was therefore investigated. A Swern oxidation of the hydroxymethyloxazolidinone **32** gave the aldehyde **57** that was oxidised further to give the carboxylic acid **58**, see Scheme 7. Activation of the acid using isobutyl chloroformate and reaction of the ensuing mixed anhydride with 2-aminopropanol gave the amide **59** as a mixture of epimers but only in a very modest yield. Nevertheless, further oxidation gave the aldehyde **60** and cyclisation under the Robinson–Gabriel conditions[16] gave the

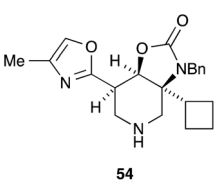
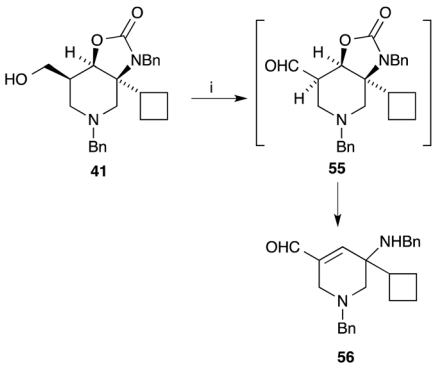
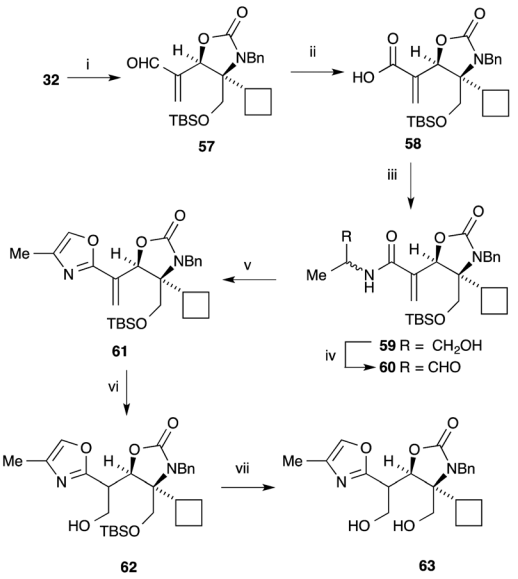


Fig. 9 The 2-(4-methyloxazol-2-yl)piperidine selected as the first 2-hetarylpiperidine for synthesis.



Scheme 6 Oxidation of the 2-hydroxymethylpiperidine **41**. Reagents and conditions (i) $(COCl)_2$, DMSO, DCM, −78 °C, 20 min, add **41**, DCM, 20 min, $^{i}Pr_2NEt$, −78 °C to rt, 3 h (93%).



Scheme 7 Approaches to the 2-oxazolylpiperidine **54**. Reagents and conditions (i) Dess–Martin periodinane, DCM, rt, 45 min; (ii) ^{t}BuOH, H_2O, 2-methylbut-2-ene, $NaClO_2$, NaH_2PO_4, rt, 2 h (*ca.* 100%); (iii) ^{i}BuOC(O)Cl, *N*-methylmorpholine, THF, rt, 1 h, add 2-aminopropanol, rt, 12 h (36%); (iv) Dess–Martin periodinane, DCM, rt, 45 min; (v) Ph_3P, 2,6-di-*tert*-butyl-4-methylpyridine, DCM, 1,2-dibromotetrachloroethane, 0 °C, 1 h, add MeCN, DBU, rt, 2.5 h (42%); (vi) BH_3.THF, THF, 0 °C, 24 h, add EtOH, NaOAc, 30% aq. H_2O_2, rt, 18 h (20%); (vii) TBAF, THF, rt, 1 h.

oxazole **61**. Hydroboration of the oxazole gave a low yield of a product provisionally identified as the alcohol **62** (exocyclic configuration not confirmed) and desilylation gave the diol **63**, but attempts to cyclise this diol *via* its bis-mesylate to the piperidine **54** using ammonia were unsuccessful. The ^{1}H NMR data of the crude products indicated that elimination had taken place analogous to the formation of the aldehyde **56** but no product was formally identified, see Scheme 7.

The instability to base of the aldehyde **55** and the difficulties encountered on attempted isolation of the 1,3-oxazole **54**, suggested that oxazolidinonylpiperidines **5** with anion stabilising groups at C2 would be sensitive to basic conditions. It was therefore decided to investigate the synthesis of the oxazolidinone-fused piperidine **64**, see Fig. 10, with a furan at C2, since the furan should be less effective than a 1,3-oxazole at acidifying H2. Following the strategy used for the synthesis of the 2-methoxymethylpiperidine **8**, it was thought that the 2-furylpiperidine **64** would be available by hydroboration of the alkenyl-1,3-oxazolidinone **65** followed by cyclisation. The oxazolidinone **65** in turn should be accessible from the aldehyde **10** by a chelation controlled addition of a vinylic Grignard reagent with subsequent side-chain modification if necessary.

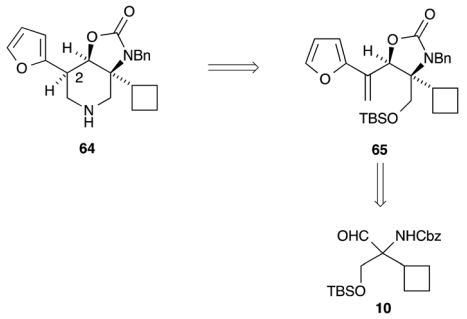


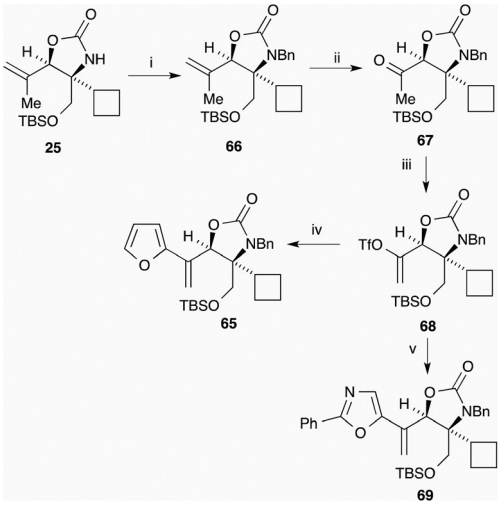
Fig. 10 Planned approach to the oxazolidinonylpiperidine **64**.

Synthesis of the 5-(furylethenyl)-1,3-oxazolidinone 65

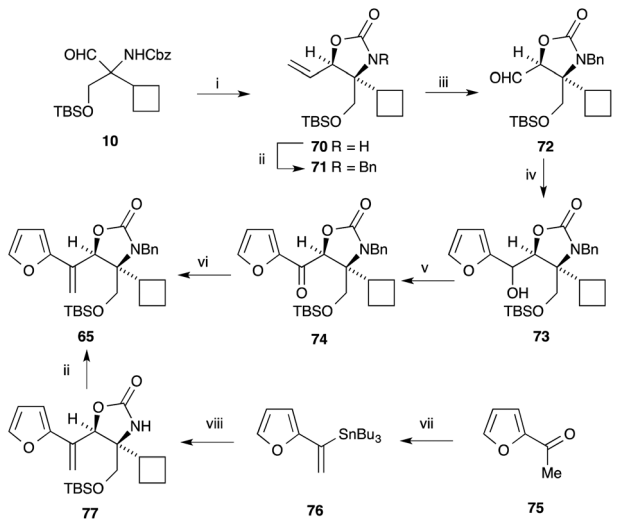
Stille couplings[17] were first investigated for the introduction of the furan. *N*-Alkylation of the oxazolidinone **25** gave the *N*-benzylated oxazolidinone **66**. Ozonolysis gave the ketone **67** that was converted into the enol triflate **68** by selective deprotonation of the methyl group and trapping the enolate so formed using phenyltriflimide.[18] Using $Pd(PPh_3)_4$ in the presence of lithium chloride and copper(1) iodide, the Stille coupling of the enol triflate **68** with 2-tributylstannylfuran gave the required alkene **65**.[19] Preliminary studies were also carried out into the Pd(0) catalysed coupling of the enol triflate with other metalated heterocycles. Thus treatment of an excess of 5-lithio-2-phenyl-1,3-oxazole[20] with zinc chloride gave the corresponding organozincate that was coupled with the triflate **68** in the presence of $PdCl_2(PPh_3)_2$ as the catalyst to give the coupled 1,3-oxazole **69** albeit in only a modest yield, see Scheme 8.

Although the Stille coupling had given the required alkene **65** quite efficiently other syntheses of this key intermediate from the aldehyde **10** were investigated. A longer synthesis, but one that avoided the use of organostannanes, proceeeded *via* the addition of ethenylmagnesium bromide to the aldehyde **10** to give the oxazolidinone **70** that was alkylated to give its *N*-benzyl derivative **71**. Ozonolysis than gave the aldehyde **72** that gave the alcohol **73** as a mixture of epimers on addition of 2-lithiofuran. Oxidation gave the ketone **74** and a Wittig reaction gave the alkene **65**, see Scheme 9.

However the most efficient conversion of the aldehyde **10** into the alkene **65** involved just two steps. Tributylstannylethenylfuran **76** was prepared from 2-acetylfuran **75** by addition of tributyltin lithium with *in situ* dehydration using



Scheme 8 Palladium(0) catalysed introduction of heteroarenes. Reagents and conditions (i) NaH, THF, BnBr, reflux, 1 h (79%); (ii) O_3, DCM, −78 °C, PPh_3, rt (93%); (iii) KHMDS, tol., −78 °C, 1 h, then add $PhNTf_2$, THF, −78 °C, 5 h (71%); (iv) $Pd(Ph_3P)_4$, LiCl, CuI, THF, 2-tributylstannylfuran, reflux 3 h (65%); (v) 5-bromo-2-phenyl-1,3-oxazole, ^{n}BuLi, THF, −18 °C, 45 min, $ZnCl_2$, THF, rt, 30 min, add to **68** and $PdCl_2(PPh_3)_2$ in THF, rt, 48 h (36%).



Scheme 9 Alternative syntheses of the alkene **65**. Reagents and conditions (i) CH_2=CHMgBr, THF, −78 °C, 2 h, then rt, 16 h (91%); (ii) NaH, BnBr, THF, 0 °C, refux, 6 h (**71**, 86%; **65**, 78% from **10**); (iii) O_3, DCM, −78 °C, Ph_3P, rt, 3 h (90%); (iv) furan, ^{n}BuLi, hexanes, −78 °C, rt, 1.5 h, cool to −78 °C, add **72**, 5 h (60%); (v) TPAP, NMO, DCM, rt, 2 h (85%); (vi) Ph_3PMeBr, ^{n}BuLi, THF, rt, 1 h, add **74**, rt, 15 min (72%); (vii) Bu_3SnLi, THF, rt, 1 h, MsCl, Et_3N, rt, 16 h (59%); (viii) **76**, ^{n}BuLi, THF, −78 °C, 10 min, add **10**, −78 °C, 20 min, rt, 16 h.

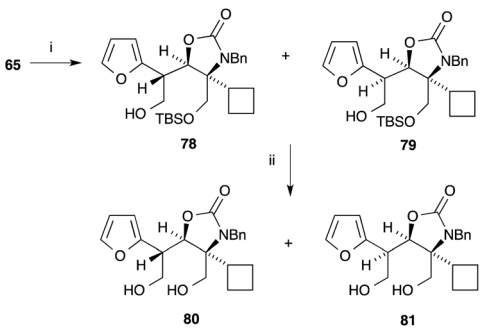
mesyl chloride.[21] Following transmetallation of the stannane **76** with *n*-butyllithium, addition of the resulting vinyllithium to the aldehyde **10** gave the 1,3-oxazolidinone 77 that was *N*-benzylated to give the alkene **65**.[13]

Conversion of the alkene 65 into oxazolidinonyl-fused piperidines

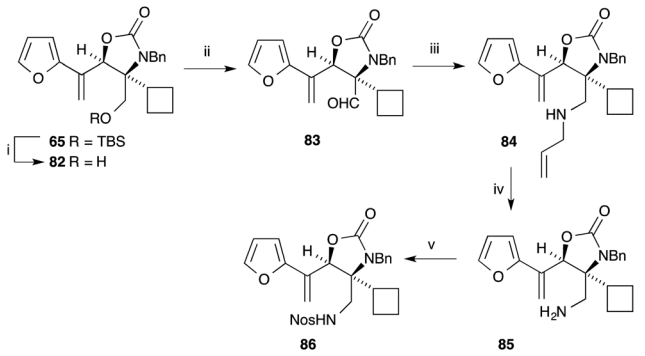
Following the procedures developed during the synthesis of the methoxymethylpiperidine **8**, it was thought that conversion of the alkene **65** into the target compound **64** would be achieved by hydroboration, desilylation to the diol, and piperidine formation *via* the corresponding bis-mesylate. However, although the hydroboration–oxidation gave the alcohols **78** and **79** as an inseparable mixture of epimers, ratio *ca.* 2 : 1 and desilylation gave the diols **80** and **81**, see Scheme 10, preliminary studies indicated that the preparation of the bis-mesylates from the diols was capricious due to competing elimination. Structures were assigned to the products **78–81** using spectroscopic data. At this point it was not known which alcohol, **78** or **79**, was the major product from the hydroboration–oxidation, although by analogy with the hydroborations of the alkenes **34** and **44** it was thought that the required isomer **79** was probably the major isomer. Subsequently this was found not to be the case, *vide infra*.

As the synthesis of the 2-furylpiperidine by displacement of bis-mesylates was proving difficult, it was decided to introduce the nitrogen of the piperidine ring before ring formation. Desilylation of the alkene **65** gave the alcohol **82** but attempts to convert this neopentylic alcohol directly into the nosylamide **86** by a Mitsunobu reaction were not succesful perhaps because of steric hindrance. Therefore the alcohol was oxidised to the aldehyde **83** that was converted into the amine **84** by reductive amination using propenylamine. A palladium(0) catalysed de-allylation[22] gave the primary amine **85** that was converted into its nosyl derivative **86**, see Scheme 11. However, attempts to hydroborate nosylamide **86** were unsuccessful, mixtures of products being isolated after oxidation. The structures were initially assigned to the products in Scheme 11 on the basis of their spectroscopic data and earlier work. The structure of the crystalline amine **84** was confirmed by X-ray crystallography, see Fig. 11.

Although the hydroboration of the alkene **86** was not successful, hydroxylation using osmium tetraoxide[23] gave a reasonable yield of a single diol **87**, see Scheme 12. The con-



Scheme 10 Hydroboration of the alkene **65**. Reagents and conditions (i) BH_3.THF, 0 °C to rt, 3 h, then $NaBO_3{\cdot}4H_2O$, rt, 16 h (60%; 2 : 1 mixture of epimers); (ii) TBAF, THF, rt, 30 min (**80**, 62%; **81**, 28%).



Scheme 11 Introduction of the neopentylic amine. Reagents and conditions (i) TBAF, THF, rt, 1 h (*ca*. 100%); (ii) Dess–Martin periodinane, DCM, rt, 2 h; (iii) prop-2-enylamine, $MgSO_4$, DCM, reflux, 16 h, then $NaCNBH_3$, THF, MeOH, HOAc, rt, 1 h (56% from **82**); (iv) $Pd(PPh_3)_4$, DCM, 1,3-dimethylbarbituric acid, 35 °C, 2 h, (74%); (v) NosCl, Et_3N, DCM, rt, 2 h (76%).

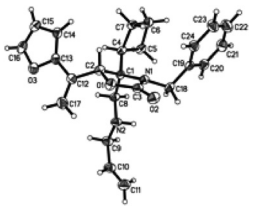
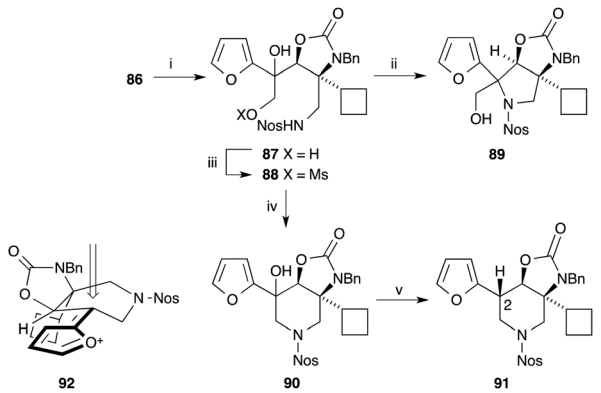


Fig. 11 The structure of the amine **84** as established by X-ray crystallography.



Scheme 12 A synthesis of the piperidine **91**. Reagents and conditions (i) OsO_4, NMO, THF, H_2O, rt, 16 h (64%); (ii) Ph_3P, DIAD, THF, rt, 16 h (73%); (iii) MesCl, py., rt, 2 h; (iv) K_2CO_3, DMF, 45 °C, 1.5 h (42% from **87**); (v) Et_3SiH, $BF_3{\cdot}Et_2O$, DCM, 0 °C, 15 min, rt, 2 h (32%).

figuration of the tertiary alcohol was not established. Nevertheless, attempts to cyclise this to a piperidine that could be converted to the target compound **64** were investigated. Using modified Mitsunobu conditions,[24] the diol **87** cyclised but gave the pyrrolidine **89** not the required piperidine **90** perhaps *via* participation of the epoxide formed by dehydration of the diol. In contrast, the mesylate **88**, prepared from the diol **87**, on treatment with mild base, cyclised directly to give the piperidine **90**.

The structure of the pyrrolidine **89** was established by ^1H NMR, the presence of an ABX system that simplified to an AB system on shaking with D_2O being assigned to the exocyclic CH_2OH fragment. No such ABX system was observed for the piperidine **90**. The structure of the piperidine **90** was consistent with its spectroscopic data but its configuration at C2 was not established.

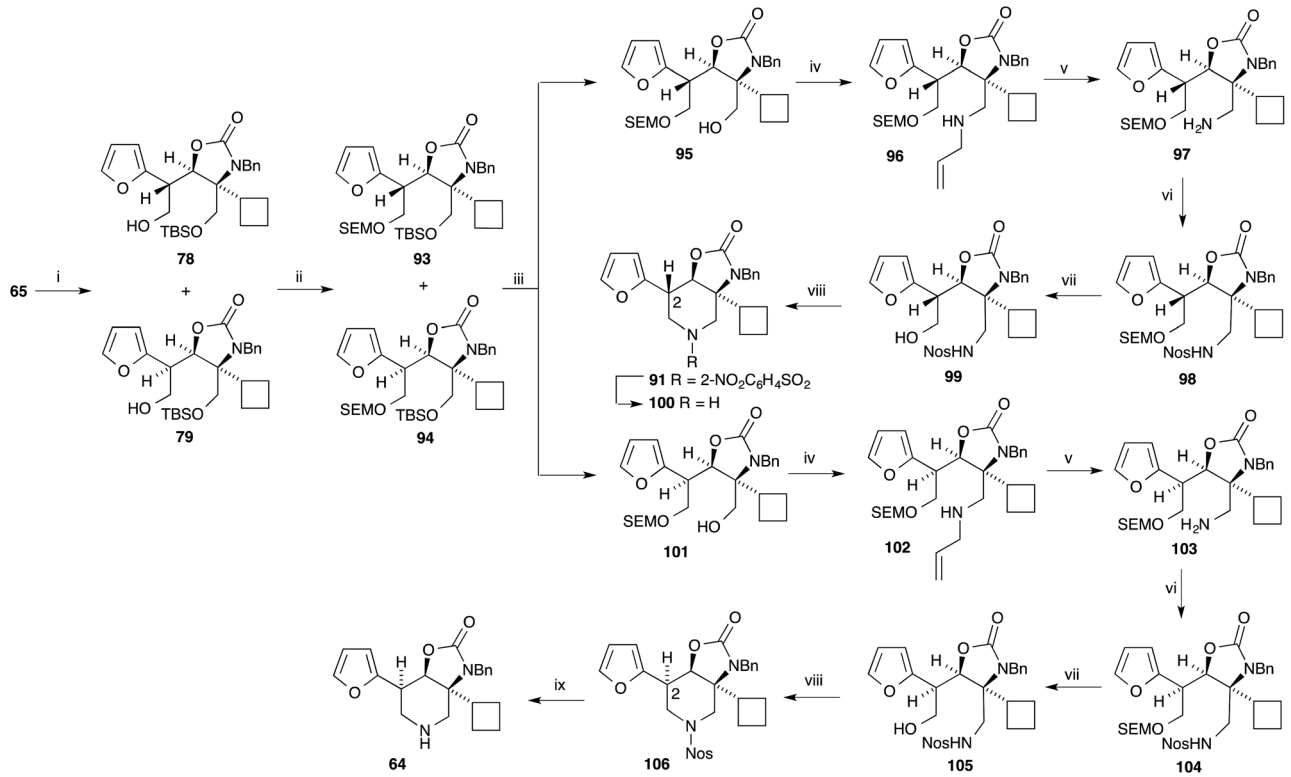
Dehydroxylation of the piperidine **90** with triethylsilane in the presence of boron trifluoride diethyletherate[25] gave a single product that was identified as the piperidine **91** on the basis of its C1–C2 coupling constant of 6.0 Hz. The formation of this epimer, that has the undesired configuration at C2, can be explained by axial addition of hydride on to the less hindered face of the boat-like oxonium ion **92** cis to the oxazolidinone ring, see Scheme 12.

At this point, it was decided to use the reductive amination sequence used to prepare the amide **86** on intermediates synthesised from the hydroboration–oxidation products **78** and **79** to prepare precursors for cyclisation to piperidines, see Scheme 13.

The hydroboration products **78** and **79** could not be separated but the mixture was reacted with SEM-chloride to convert the free alcohols into the corresponding SEM-ethers **93** and **94**. These were desilylated to give the the alcohols **95** and **101**, ratio 2 : 1, that could be separated. At this stage it was not known which alcohol, **95** or **101**, was the major product. However, when the major product was taken through the synthesis it led to the undesired piperidine **91** and so was identified as the epimer **95**, see Scheme 13.

Thus reductive amination of the aldehyde prepared by oxidation of the major alcohol **95** gave the amine **96**. Deallylation and nosylation of the resulting amine **97** gave the amide **98** that was deprotected to give the alcohol **99**. This cleanly cyclised using the Mitsunobu protocol but gave the piperidine **91** that had already been prepared by dehydroxylation of the hydroxypiperidine **90** and which had been identified as the C2 epimer of the required piperidine on the basis of its C1–C2 coupling constant of 6 Hz. Denosylation gave the deprotected piperidine **100**.

The formation of piperidine **91** from this sequence showed that the alcohol **78** was the major product of hydroboration–oxidation of the alkene **65**. This was surprising since, by analogy with earlier work, isomer **79** had been expected to be the major product. It would appear that the hydroboration of the alkene **65** occurred preferentially on the opposite face from that observed for the alkoxymethyl alkenes **34** and **44**, possibly *via* transition structure **107**, see Fig. 12, *cf*. transition structure **42** in Fig. 6. The required hydroboration product **79** was only the minor product from hydroboration of the alkene at 0 °C. However, when the hydroboration was repeated at higher temperatures, the stereoselectivity dropped and at 35 °C the ratio of the two products **78** and **79** was approximately 1 : 1.



Scheme 13 Synthesis of the piperidines **64** and **100**. Reagents and conditions (i) BH_3.THF, 0 °C, 3 h or warm to 35 °C, 3 h , NaOH, H_2O_2, rt, 30 min (0 °C, 60%, **78** : **79** = 2 : 1; 35 °C, 65%, **78** : **79** *ca.* 1 : 1); (ii) **78** and **79**, SEMCl, DMAP, TBAI, $^{i}Pr_2NEt$, rt , 16 h (*ca.* 99%); (iii) **93** and **94**, ratio *ca.* 1 : 1, TBAF, THF, rt, 16 h (95, 43%; 101, 36%); (iv) (a) Dess–Martin periodinane, DCM , rt , 2 h (b) prop-2-enylamine, $MgSO_4$, DCM , reflux , 16 h (c) $NaCNBH_3$, MeOH, HOAc, THF, rt , 1 h (**96**, 73%; **102**, 70%); (v) $Pd(PPh_3)_4$, 1,3-dimethylbarbituric acid, DCM , 35 °C, 2 h; (vi) NosCl, Et_3N , rt, 2 h (**98**, 60%; **104**, 70%); (vii) $MgBr_2$, nitromethane, ether, rt, 2 h (**99**, 77%; **105**, 75%); (viii) Ph_3P, DIAD, THF, rt, 2 h (**91**, 73%; **106**, 80%); (ix) K_2CO_3, PhSH, acetonitrile, rt, 2 h (**100**, 75%; **64**, 86%).

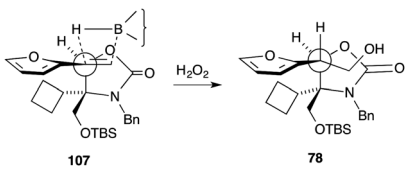


Fig. 12 The facial selectivity of hydroboration of alkene **65**.

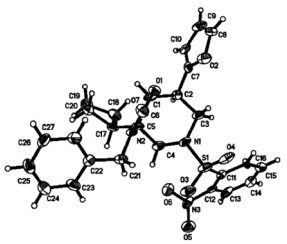


Fig. 13 The structure of the *N*-nosylpiperidine **106** as established by X-ray crystallography.

Although not ideal, this mixture was taken through the synthesis. Thus reaction with trimethylsilylethoxymethyl chloride gave a mixture of the SEM-ethers **93** and **94** that were selectively desilylated to give the alcohols **95** and **101**, ratio *ca.* 1 : 1, that were separated. The required epimer **101** was then taken through to the *N*-nosylpiperidine **106** by oxidation and reductive amination of the intermediate aldehyde to give the primary amine **103** after deallylation. Following *N*-nosylation and SEM-deprotection, cyclisation to the required *N*-nosylpiperidine **106** was carried out using a Mitsunobu reaction. Denosylation then gave the required oxazolidinonylpiperidine **64**. The structures of the piperidines **64** and **106** were consistent with their C1–C2 coupling constants of *ca.* 1.6 Hz. Moreover the *N*-nosylpiperidine **106** was crystalline and its structure was confirmed by X-ray crystallography, see Fig. 13.

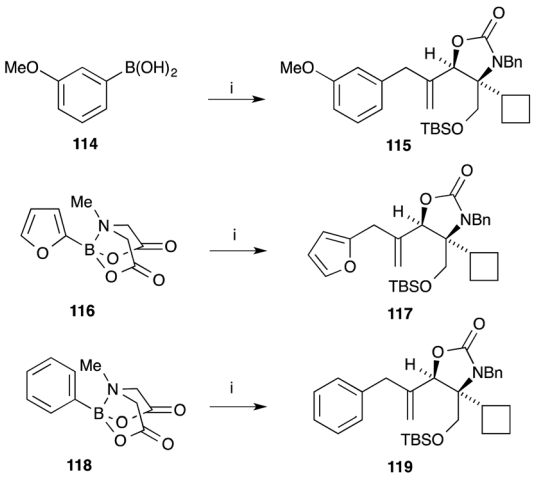
The stability of the 2-furyloxazolidinonylpiperidine **64** was consistent with the hypothesis that the earlier problems in preparing oxazole **54** had been due to the increase in the acidity of H2. Therefore, it was decided to study oxazolidinonyl-fused piperidines with arylmethyl and heteroarylmethyl substituents at C2 since these substituents should be less effective in acidifying H2 and a wider range of heteroaryl groups should be tolerated.

Synthesis of oxazolidinonyl-fused piperidines with 2-(heteroarylmethyl)- and 2-(arylmethyl)-substituents

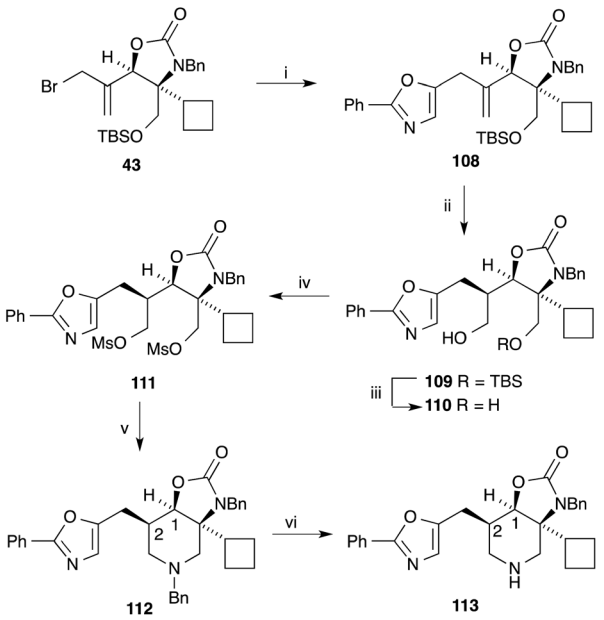
A synthesis of the oxazolidinonyl-fused piperidine with a 2-(2-phenyl-1,3-oxazol-5-yl)methyl substituent is outlined in Scheme 14. 5-Bromo-2-phenyloxazole[20] was reacted with *n*-butyllithium to effect bromine–lithium exchange and the organolithium species so formed was alkylated using the bromide **43** in the presence of copper(I) cyanide/lithium chloride to give the oxazole **108**. Hydroboration of this alkene required stirring at room temperature overnight, but was still usefully stereoselective, 9 : 1, in favour of the epimer **109** after oxidation. Desilylation gave the diol **110** that was converted to the bis-mesylate **111**. Reaction with benzylamine gave the piperidine **112** and transfer hydrogenolysis gave the required 2-(2-phenyloxazol-5-ylmethyl)piperidine **113**, see Scheme 14.

The structures of the products in Scheme 14 were assigned on the basis of their spectroscopic data. Of note is the stereoselectivity of the hydroboration of the alkene **108**. The configuration shown was assigned on the basis of the H1–H2 coupling constant observed for piperidines **112** and **113** that were in the range 2.0–2.5 Hz diagnostic of the required configuration at C2.

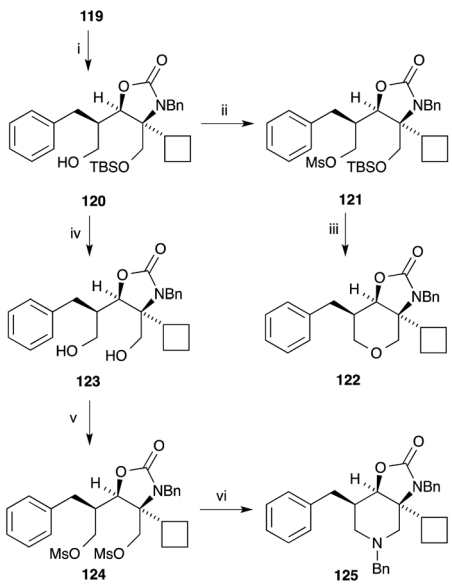
Although the coupling of 5-lithiated 2-phenyl-1,3-oxazole with the bromide **43** had given a good yield of the alkene **108**, alternative coupling procedures were investigated based on the Suzuki–Miyaura coupling of bromide **43** with commercially available boronic acids and derivatives.[26] With 3-methoxyphenylboronic acid **114**, a good yield of the alkene **115** was obtained using $(Ph_3P)_2PdCl_2$ as the catalyst. However, the use of furylboronic acid was more capricious in our hands, perhaps because of the acid sensitivity of the furylboronic acid, and better yields of the alkene **117** were obtained using the MIDA-boronate **116** again with $(Ph_3P)_2PdCl_2$ as the catalyst and sodium carbonate as the base.[27] The same conditions gave a good yield of the alkene **119** using the phenyl-MIDA boronate **118**, see Scheme 15.



Scheme 15 Suzuki–Miyaura coupling of the bromide **43**. Reagents and conditions (i) **43**, $(Ph_3P)PdCl_2$ (cat.), Na_2CO_3, THF, H_2O, reflux, 3–12 h (**115**, 73%; **117**, 72%; **119**, 73%).



Scheme 14 Synthesis of the 2-(2-phenyl-1,3-oxazolyl-5-ylmethyl) piperidine **113**. Reagents and conditions (i) 5-bromo-2-phenyloxazole, ^{n}BuLi, THF, –18 °C, 45 min, cooled to –40 °C, CuCN, LiCl, THF, 1 h, add **43**, THF, 18 h (80%); (ii) BH_3.THF, 0 °C to rt, 24 h, EtOH, NaOAc, 30% aq. H_2O_2, heat under reflux 1.5 h (50%; 9 : 1 mixture of epimers); (iii) TBAF, THF, 0 °C to rt, 1 h (83%); (iv) MsCl, DCM, Et_3N, 0 °C to rt, 1 h; (v) $BnNH_2$, 90 °C, 18 h (81% from **110**; a 9 : 1 mixture of epimers); (vi) 10% Pd/C, HCO_2H, MeOH, rt, 20 min (54%).



Scheme 16 Synthesis of the 2-benzyltetrahydropyran **122** and the 2-benzylpiperidine **125**. Reagents and conditions (i) BH_3.THF, 0 °C to rt, 16 h, EtOH, NaOAc, 30% aq. H_2O_2, heat under reflux 1.5 h (73%); (ii) Et_3N, MsCl, DCM, 0 °C to rt, 1 h; (iii) TBAF, THF, 0 °C to rt, 1 h (56% from **120**); (iv) TBAF, THF, 0 °C to rt, 1 h (72%); (v) Et_3N, MsCl, DCM, 0 °C to rt, 1 h; (vi) $BnNH_2$, 90 °C, 18 h (64% from **123**).

Preliminary studies were undertaken into the hydroboration and cyclisation of the alkene **119**. Hydroboration–oxidation gave the alcohol **120** selectively. In this case two cyclisation procedures were studied. Mesylation of the alcohol **120** followed by desilylation of the mesylate **121** using TBAF was accompanied by *in situ* cyclisation and gave the tetrahydropyran **122** as a single diastereoisomer, the configuration at C2 following from the H1–H2 coupling constant of 2.5 Hz and from nOe studies. In contrast, desilylation of the monoprotected diol **120** gave the diol **123** that was mesylated and reaction of the resulting bis-mesylate **124** with benzylamine gave the piperidine **125**, the configuration at C2 again being confirmed by the H1–H2 coupling constant of 2.0 Hz, see Scheme 16.

Summary and conclusions

This work has resulted in the synthesis of several oxazolidinonyl-fused piperidines of interest as possible agonists of muscarinic M_1 receptors and has opened up access to this class of piperidines. Indeed the 2-(methoxymethyl)piperidine **8** was a 50% partial agonist of the M_1 receptor with micromolar potency as measured by the relaxation responses of rat duodenum compared with the full agonist McN-A-343. Significant preliminary studies also indicated that the 2-furylpiperidine **64** was a positive allosteric modulator of the muscarinic M_1 receptor as it potentiates the effects of an M_1 receptor agonist without causing agonist or antagonistic activity on its own, see Experimental and ESI.‡

Of interest in the synthetic work was the stereoselectivities observed for the addition of vinylic Grignard reagents to the aldehyde **10**. These were accompanied by *in situ* cyclisation to give oxazolidinones directly. Also of note was the stereoselectivity observed for the hydroboration–oxidation of the 5-alkenyloxazolidinones. In most cases, at lower temperatures, the selectivity was consistent with the transition structure **42** shown in Fig. 6, but when a heteroaromatic ring was directly attached to the double-bond the stereoselectivity was reversed, consistent with transition structure **107**, see Fig. 12. Molecular modelling studies were not carried out to probe the subtle factors involved in the stereoselectivities of these reactions, transition structures **42** and **107** are just suggested as consistent with the observed stereoselectivities. However, in the latter case the stereoselectivity was reduced when higher temperatures were used and the synthesis of the 2-furylpiperidine **64** could be completed.

During the synthetic work, it was found that oxazolidinonylpiperidines with substituents at C2 that were able to facilitate deprotonation were unstable with respect to oxazolidinone ring-opening and loss of CO_2. This limited the nature of the heterocyclic group that could be accommodated at this position. In order to broaden the scope of heteroaromatic substituents at C2, the synthesis of oxazolidinonylpiperidines with 2-heterarylmethyl and 2-arylmethyl substituents at C2 was undertaken since the methylene group would separate the heteroaromatic ring from H2 and so discourage the elimination process. This work was successful.

During these studies, compounds were prepared that showed agonistic effects for the M_1 muscarinic receptor. However, the syntheses involved were fairly challenging and limited the number of compounds that could be prepared although it should be possible to improve and shorten the synthesis of any compound considered to be worthy of further investigation. Moreover, simpler analogues with alternative substituents, *e.g.* an isopropyl group rather than the cyclobutyl group at C6, should be significantly more accessible, and so the study of the effect of different alkyl groups at this site is of interest. The allosteric activity of the piperidine **64** is clearly worth further investigation. Finally, this work has contributed to methodology for the synthesis of piperidines.[28]

Experimental

General experimental details

^{1}H and ^{13}C NMR spectra were recorded on Varian Unity Inova 400 and Varian Unity Inova 300 spectrometers with residual non-deuterated solvent as the internal standard. Only distinguishable peaks are reported for minor isomers in isomeric mixtures. IR spectra were recorded on an ATI Mattson Genesis FTIR as thin films produced by evaporation of a dichloromethane solution on sodium chloride plates unless otherwise stated. Mass spectra were recorded on Fison VG Trio 2000 and Kratos Concept spectrometers. Chemical ionisation (CI^+) was performed using ammonia. Chromatography refers to flash column chromatography using Merck silica gel 60 H (230–300 mesh). Tetrahydrofuran (THF) was dried and distilled from sodium metal using benzophenone as an indicator under an atmosphere of nitrogen. Dichloromethane was dried and distilled from calcium hydride under an atmosphere of nitrogen. Ether refers to diethyl ether, which was dried and distilled from sodium metal using benzophenone as an indicator under an atmosphere of nitrogen. Light petroleum refers to the fraction of petroleum ether distilled between 40–60 °C. Benzene and hexane were dried over sodium metal. Butyllithium (1.6 M in hexanes) was titrated against a solution of propan-2-ol in xylene with 2,2′-bipyridine as an indicator. Triethylamine and di-isopropylamine were dried over potassium hydroxide pellets. Brine refers to saturated aqueous sodium chloride.

1-Cyclobutyl-2-hydroxyethanone (15). A solution of the bromoketone **14**[10] (56.8 g, 320 mmol) and potassium formate (67.5 g, 802 mmol, 2.5 eq.) in methanol (700 mL) was heated under reflux for 12 h then concentrated under reduced pressure. Ether was added and precipitated KBr was removed by filtration. Concentration under reduced pressure gave the title compound **15** (26 g, 71%), R_f = 0.23 (ethyl acetate : light petroleum = 1 : 4) (Found: $M^+ + NH_4$, 132.1021. $C_6H_{14}NO_2$ requires *M*, 132.1024); ν_{max}/cm^{-1} 3424, 2977, 2944, 2865, 1709, 1460, 1351, 1246, 1075, 982 and 911; δ_H (300 MHz, $CDCl_3$) 1.85–2.37 (6 H, m, 3 × CH_2), 3.29 (1 H, pent, *J* 8.2 Hz, 1′-H) and

4.22 (2 H, s, 2-H_2); δ_C (75 MHz, $CDCl_3$) 18.3, 24.5, 41.4, 66.1 and 210.6; *m*/*z* (CI^+) 132 (M^+ + 18, 50%), 115 (M^+ + 1, 10) and 55 (100).

2-*tert*-Butyldimethylsilyloxy-1-cyclobutylethanone (11). A solution of the alcohol **15** (26 g, 228 mmol), TBSCl (37.6 g, 250 mmol, 1.1 eq.), imidazole (31.2 g, 456 mmol, 2 eq.) DMAP (trace) and TBAI (trace) in DCM (500 mL) was stirred at rt for 1 h. Water (200 mL) was added and the aqueous phase was extracted with ether (3 × 150 mL). The organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography (ethyl acetate : light petroleum = 1 : 30) of the residue gave the title compound **11** (32.25 g, 62%), R_f = 0.64 (ethyl acetate : light petroleum = 1 : 4) (Found: M^+ + H, 229.1621. $C_{12}H_{25}O_2Si$ requires *M*, 229.1624); ν_{max}/cm^{-1} 2951, 2859, 1712, 1471, 1434, 1390, 1360, 1344, 1258, 1171, 1108, 1048, 1007, 939, 912, 841, 778 and 736; δ_H (300 MHz, $CDCl_3$) 0.07 (6 H, s, 2 × $SiCH_3$), 0.91 [9 H, s, $SiC(CH_3)_3$], 1.71–2.36 (6 H, m, 3 × CH_2), 3.49 (1 H, pent, *J* 8.2 Hz, 1′-H) and 4.18 (2 H, s, 2-H_2); δ_C (75 MHz, $CDCl_3$) −5.6, 18.2, 18.3, 24.2, 25.7, 41.6, 67.8 and 211.4; *m*/*z* (CI^+) 246 (M^+ + 18, 27%) and 229 (M^+ + 1, 100%).

(*Z*)- and (*E*)-4-*tert*-Butyldimethylsilyloxy-3-cyclobutylbut-2-en-1-ols [(*Z*)- and (*E*)-17]. Triethylphosphonoacetate (13.65 mL, 68.7 mmol, 1.1 eq.) was added to a suspension of sodium hydride (60% in mineral oil, 2.75 g, 68.7 mmol, 1.1 eq.) in THF (250 mL) and the reaction mixture stirred at rt for 45 min. The ketone **11** (14.27 g, 62.5 mmol) in THF (40 mL) was added and the reaction mixture stirred at rt for 2.5 h. Saturated aqueous ammonium chloride (100 mL) was added and the aqueous layer extracted with ether (3 × 150 mL). The organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure to give a mixture of the (*Z*)- and (*E*)-alkenes **16** (18.66 g, 100%), R_f = 0.63 and 0.57 (ethyl acetate : light petroleum = 1 : 4).

Di-isobutylaluminium hydride (1.0 M in hexanes, 162 mL, 162 mmol, 2.6 eq.) was added dropwise to the mixture of esters **16** (18.66 g, 62.5 mmol) in THF (45 mL) at −78 °C. After 3 h, the solution was allowed to warm to 0 °C and stirred for a further 30 min. Water (4.25 mL) was added at 0 °C followed by saturated aqueous potassium sodium tartrate (162 mL) and ether (162 mL). The reaction mixture was then allowed to warm to rt and the aqueous layer was extracted with ether (3 × 160 mL). The organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography (ethyl acetate : light petroleum = 1 : 10) of the residue gave the (*Z*)- and (*E*)-title compounds (*Z*)- and (*E*)-**17** (14.4 g, 89%) as a colourless oil, ratio (*Z*)-**17** : (*E*)-**17** = 75 : 25 (^{1}H NMR) from which a sample of the major (*Z*)-isomer (*Z*)-**17** was isolated, R_f = 0.42 (ethyl acetate : light petroleum = 1 : 4); ν_{max}/cm^{-1} 3359, 2955, 2932, 2885, 2859, 1471, 1389, 1361, 1254, 1088, 1007, 982, 839 and 776; δ_H (300 MHz, $CDCl_3$) 0.09 (6 H, s, 2 × $SiCH_3$), 0.91 [9 H, s, $SiC(CH_3)_3$], 1.65–2.13 (7 H, m, 3 × CH_2, OH), 3.04 (1 H, pent, *J* 8.8 Hz, 3-CH), 4.14 (2 H, s, 4-H_2), 4.20 (2 H, t, *J* 6.2 Hz, 1-H_2) and 5.54 (1 H, t, *J* 7.0 Hz, 2-H); δ_C (75 MHz, $CDCl_3$) −5.4, 17.8, 18.3, 25.9, 27.5, 39.9, 58.8, 60.3, 123.6 and 145.9; *m*/*z* (CI^+) 274 (M^+ + 18, 2%) and 239 (M^+ + 1, 100); minor (*E*)-isomer (*E*)-**17** δ_H (300 MHz, $CDCl_3$) 2.24 (1 H, br. s, OH), 3.31 (1 H, pent, *J* 9.2 Hz, 3-CH) and 5.57 (1 H, t, *J* 6.2 Hz, 2-H); δ_C (75 MHz, $CDCl_3$) 18.3, 19.2, 28.0, 35.9, 64.3, 122.8 and 143.2.

(*Z*)- and (*E*)-4-*tert*-Butyldimethylsilyloxy-3-cyclobutylbut-2-en-1-yl trifluoroacetimidates [(*Z*)- and (*E*)-18]. An intimate mixture of powdered trifluoroacetamide (75 g, 663 mmol) and phosphorous pentoxide (150 g, 528 mmol, 0.80 eq.) was prepared in a 2 L round bottom flask fitted with a water cooled condenser, from the top of which led a PTFE tube to a trap cooled in a −78 °C bath. This trap was connected to a second trap cooled to −115 °C (ether/N_2) which was attached to a cold finger. A calcium chloride tube protected the end of this trap from moisture. This was connected to a scrubber bath containing aqueous sodium hydroxide. The reaction mixture, under a gentle stream of dry nitrogen, was gradually warmed to 150 °C and this temperature was maintained for 5 h. Trifluoroacetonitrile was collected as a colourless liquid. Cooled THF (100 mL) at −78 °C, was then added to the condensed trifluoroacetonitrile.

Sodium hydride (1.5 g, 37.5 mmol, 1 eq., 60% in mineral oil) was added to a mixture of the alcohols (*Z*)- and (*E*)-**17** (9.2 g, 35.7 mmol) in THF (200 mL). The mixture was stirred at rt for 1 h then cooled to −78 °C and added to the solution of trifluoroacetonitrile in THF at −115 °C. The reaction mixture was warmed to −78 °C, stirred for 1 h, then warmed to rt and nitrogen was bubbled through it for 45 min to purge the excess of the trifluoroacetonitrile. Ammonium chloride (5 g) was added and the mixture was diluted with light petroleum (400 mL) then filtered through celite. Concentration of the filtrate under reduced pressure gave a mixture of the title compounds (*Z*)- and (*E*)-**18** (11.1 g, 88%). Chromatography (ethyl acetate : light petroleum = 1 : 20) gave a sample of the mixture for characterisation, R_f = 0.27 (ethyl acetate : light petroleum = 1 : 25) (Found: M^+ + H, 352.1922. $C_{16}H_{29}NO_2F_3Si$ requires *M*, 352.1920); ν_{max}/cm^{-1} 3355, 2956, 2933, 2895, 2859, 1685, 1472, 1256, 1202, 1166, 1077, 837 and 776; δ_H (400 MHz, $CDCl_3$) major (*Z*)-isomer (*Z*)-**18** 0.07 (6 H, s, 2 × $SiCH_3$), 0.90 [9 H, s, $SiC(CH_3)_3$], 1.70–2.15 (6 H, m, 3 × CH_2), 3.12 (1 H, pent, *J* 8.5 Hz, 3-CH), 4.17 (2 H, s, 4-H_2), 4.90 (2 H, d, *J* 6.7 Hz, 1-H_2), 5.43 (1 H, t, *J* 6.7 Hz, 2-H) and 8.14 (1 H, br. s, NH); minor (*E*)-isomer (*E*)-**18** 0.09 (6 H, s, 2 × $SiCH_3$), 0.93 [9 H, s, $SiC(CH_3)_3$], 3.36 (1 H, pent, *J* 9.0 Hz, 3-CH), 4.20 (2 H, s, 4-H_2), 4.81 (2 H, d, *J* 7.2 Hz, 1-H_2), 5.65 (1 H, tq, *J* 7.2, 1.7 Hz, 2-H) and 8.12 (1 H, br. s, NH); δ_C (100 MHz, $CDCl_3$) major (*Z*)-isomer (*Z*)-**18** −5.5, 17.9, 19.2, 25.9, 27.6, 39.5, 60.2, 64.3, 115.6 (q, *J* 279 Hz), 116.8, 148.4 and 157.6 (q, *J* 37 Hz); minor (*E*)-isomer (*E*)-**18** −5.4, 18.3(2), 25.9, 27.9, 36.0, 64.0, 64.1, 115.5 (q, *J* 249 Hz), 116.3, 147.0 and 158.0 (q, *J* 38 Hz); δ_F (375 MHz, $CDCl_3$) major (*Z*)-isomer (*Z*)-**18** −70.91; minor (*E*)-isomer (*E*)-**18** −70.97 *m*/*z* (CI^+) 352 (M^+ + 1, 2%) and 239 (100).

***N*-(1-*tert*-Butyldimethylsilyloxy-2-cyclobutylbut-3-en-2-yl) 2,2,2-trifluoroacetamide (19).** The mixture of trifluoroacetimidates (*Z*)- and (*E*)-**18** (11.1 g, 31.6 mmol) in xylene (900 mL) was heated under reflux for 18 h then cooled to rt. The xylene was removed by distillation under reduced pressure to give the title compound **19** (10.1 g, 91%), R_f = 0.29 (ethyl acetate : hexane =

1 : 25) (Found: M^+ + H, 352.1913. $C_{16}H_{29}NO_2F_3Si$ requires *M*, 352.1920); ν_{max}/cm^{-1} 3444, 3391, 3090, 2955, 2933, 2887, 2861, 1733, 1641, 1530, 1469, 1330, 1258, 1214, 1163, 1100, 1005, 922, 839, 779 and 721; δ_H (400 MHz, $CDCl_3$) 0.06 and 0.07 (each 3 H, s, $SiCH_3$), 0.90 [9 H, s, $SiC(CH_3)_3$], 1.69–2.00 (6 H, m, 3 × CH_2), 3.05 (1 H, pent, *J* 9.0 Hz, 2′-CH), 3.68 and 3.76 (each 1 H, d, *J* 9.7 Hz, 1′-H), 5.11 (1 H, d, *J* 17.5 Hz, 4′-H), 5.30 (1 H, d, *J* 11.0 Hz, 4′-H′), 5.93 (1 H, dd, *J* 11.0, 17.5 Hz, 3′-H) and 6.52 (1 H, br. s, NH); δ_C (75 MHz, $CDCl_3$) −5.8(2), 17.7, 18.0, 23.3, 23.4, 25.6, 40.0, 62.5, 64.2, 115.6, 115.8 (q, *J* 290 Hz), 135.0 and 156.0 (q, *J* 36 Hz); δ_F (375 MHz, $CDCl_3$) −74.8; *m*/*z* (CI^+) 352 (M^+ + 1, 100%). Attempted purification *via* flash chromatography led to partial decomposition.

1-*tert*-Butyldimethylsilyloxy-2-cyclobutylbut-3-en-2-ylamine (20). Sodium borohydride (8 g, 214 mmol, 7.5 eq.) was added to the trifluoroacetamide **19** (10.1 g, 28.8 mmol) in ethanol (85 mL) at 0 °C and the reaction mixture allowed to warm to rt and stirred for 18 h. More sodium borohydride (5 g, 134 mmol, 4.6 eq.) was added and the resulting slurry was stirred at rt for 6 h. Saturated aqueous sodium hydrogen carbonate (85 mL) was added and the mixture was extracted with ether (3 × 100 mL). The organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography (ethyl acetate : light petroleum = 1 : 20 to 3 : 2) of the residue gave the title compound **20** (5.92 g, 80%), R_f = 0.12 (ethyl acetate : light petroleum = 1 : 2) (Found: M^+ + H, 256.2096. $C_{14}H_{30}NOSi$ requires *M*, 256.2097); ν_{max}/cm^{-1} 3378, 3083, 2955, 2930, 2895, 2857, 1472, 1463, 1361, 1256, 1102, 1006, 918, 837 and 776; δ_H (400 MHz, $CDCl_3$) 0.02 and 0.03 (each 3 H, s, $SiCH_3$), 0.88 [9 H, s, $SiC(CH_3)_3$], 1.65–1.92 (6 H, m, 3 × CH_2), 2.52 (1 H, m, 2-CH), 3.32 and 3.38 (each 1 H, d, *J* 9.2 Hz, 1-H), 5.13 (1 H, dd, *J* 10.7, 1.5 Hz, 4-H), 5.19 (1 H, dd, *J* 17.5, 1.5 Hz, 4-H′) and 5.83 (1 H, dd, *J* 10.7, 17.5 Hz, 3-H); δ_C (100 MHz, $CDCl_3$) −5.5, 17.6, 18.2, 22.6, 22.8, 25.8, 41.5, 58.2, 68.9, 113.6 and 141.5; *m*/*z* (CI^+) 256 (M^+ + 1, 100%).

***N*-Benzyloxycarbonyl-1-*tert*-butyldimethylsilyloxy-2-cyclobutylbut-3-en-2-ylamine (21).** Benzyl chloroformate (36 mL, 255 mmol, 11 eq.) and Et_3N (10 mL, 69.5 mmol, 3 eq.) were added to the amine **20** (5.92 g, 23.2 mmol) in DCM (36 mL) at rt and the reaction mixture was stirred at rt for 18 h. Saturated aqueous sodium hydrogen carbonate (70 mL) was added and the aqueous layer was extracted with ether (3 × 80 mL). The organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography (ethyl acetate : light petroleum = 1 : 30 to 1 : 20) of the residue gave the title compound **21** (7.51 g, 83%), R_f = 0.65 (ethyl acetate : light petroleum = 1 : 4) (Found: M^+ + H, 390.2468. $C_{22}H_{36}NO_3Si$ requires *M*, 390.2464); ν_{max}/cm^{-1} 3445, 3359, 3087, 3067, 3033, 2952, 2933, 2887, 2858, 1733, 1498, 1467, 1410, 1252, 1102, 1005, 917, 839, 777 and 738; δ_H (300 MHz, $CDCl_3$) 0.02 and 0.03 (each 3 H, s, $SiCH_3$), 0.88 [9 H, s, $SiC(CH_3)_3$], 1.61–1.94 (6 H, m, 3 × CH_2), 2.93 (1 H, pent, *J* 8.5 Hz, 2-CH), 3.69 and 3.80 (each 1 H, d, *J* 9.5 Hz, 1-H), 4.91 (1 H, br. s, NH), 5.06 (2 H, s, $PhCH_2$), 5.10 (1 H, d, *J* 17.5 Hz, 4-H), 5.24 (1 H, d, *J* 11.0 Hz, 4-H′), 5.90 (1 H, dd, *J* 11.0, 17.5 Hz, 3-H) and 7.29–7.38 (5 H, m, ArH); δ_C (75 MHz, $CDCl_3$) −5.6, 17.6, 18.2, 23.0, 23.1, 25.8, 40.3, 61.0, 64.3, 66.2, 114.6, 128.0, 128.1, 128.5, 136.7, 137.3 and 154.9; *m*/*z* (CI^+) 391 (80%), 390 (M^+ + 1, 75) and 282 (100).

Carbon tetrabromide (39.6 g, 119 mmol) in dichloromethane (93 mL) was added to the carbamates (*Z*)- and (*E*)-**23** (12.75 g, 42.6 mmol) and triphenylphosphine (27.94 g, 106.5 mmol) in dichloromethane (536 mL) at −10 °C and the reaction mixture was stirred at −10 °C for 1 h. After washing with saturated aqueous $NaHCO_3$ and brine, the solution was dried ($MgSO_4$) and concentrated under reduced pressure. The residual oil was immediately dissolved in fresh tetrahydrofuran (180 mL) and powdered 4 Å molecular sieves (22 g) were added. Sodium benzyloxide [freshly prepared from benzyl alcohol (8.8 mL, 85 mmol) and NaH (3.4 g, 85 mmol) in THF (375 mL)] was added at 0 °C and the reaction mixture was stirred at room temperature for 1 h. After diluting with ethyl acetate, the solution was washed with saturated aqueous NH_4Cl and brine, then dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue (0–10% ether/light petroleum) gave the title compound **21** (13.75 g, 83%) as a colourless oil, R_f 0.65 (20% ether/light petroleum) (Found: M^+ + Na, 412.2274. $C_{22}H_{35}O_3NNaSi$ requires *M*, 412.2278) with spectroscopic data as obtained previously.[2]

4-*tert*-Butyldimethylsilyloxy-3-cyclobutylbut-2-enyl carbamate [(*Z*)- and (*E*)-23]. Trichloroacetyl isocyanate (190 μL, 1.6 mmol) was added to the alcohols (*Z*)- and (*E*)-**17** (200 mg, 0.8 mmol) in dichloromethane (5 mL) at 0 °C and the reaction mixture was stirred at this temperature for 1 h. After concentration under reduced pressure, the residue was immediately taken up in methanol (5 mL) and water (2.7 mL) and the solution was cooled to 0 °C. Potassium carbonate (330 mg, 1.7 mmol) was added and the reaction mixture was stirred at rt for 3 h. After concentration under reduced pressure, chromatography of the residue (20% ether/light petroleum) gave the title compounds (*Z*)- and (*E*)-**23** (170 mg, 70%) as a colourless oil, (*Z*) : (*E*) = 3 : 1; R_f 0.20 (20% ethyl acetate/light petroleum) (Found: M^+ + Na, 322.1815. $C_{15}H_{29}NO_3NaSi$ requires *M*, 322.1809); ν_{max}/cm^{-1} 3344, 2929, 2856, 1718, 1472, 1400, 1329, 1253, 1053, 836 and 776; δ_H (500 MHz, $CDCl_3$) (*Z*)-isomer 0.07 (6 H, s, 2 × $SiCH_3$), 0.92 [9 H, s, $SiC(CH_3)_3$], 1.67–2.09 (6 H, m, 3 × CH_2), 3.34 (1 H, m, 3-CH), 4.17 (2 H, s, 4-H_2), 4.60 (2 H, d, *J* 7.0 Hz, 1-H_2), 4.8 (2 H, br. s, NH_2) and 5.53 (1 H, dt, *J* 7.0, 1.6 Hz, 2-H); (*E*)-isomer 0.06 (6 H, s, 2 × $SiCH_3$), 0.89 [9 H, s, $SiC(CH_3)_3$], 3.11 (1 H, m, 3-CH), 4.15 (2 H, s, 4-H_2), 4.67 (2 H, d, *J* 7.0 Hz, 1-H_2), 5.33 (1 H, t, *J* 7.0 Hz, 2-H) δ_C (75 MHz, $CDCl_3$) (*Z*)-isomer −5.4, 18.2, 19.2, 25.8, 27.6, 39.3, 59.8, 61.5, 118.0, 147.4 and 156.9; *m*/*z* (ES^+) 322 (M^+ + 23, 100%).

2-Benzyloxycarbonylamino-3-*tert*-butyldimethylsilyloxy-2-cyclobutylpropanal (10). A mixture of ozone and oxygen was bubbled through a solution of the alkene **21** (7.84 g, 20.1 mmol) in DCM (220 mL) at −78 °C until the reaction mixture turned blue. Triphenylphosphine (6.35 g, 24.1 mmol, 1.2 eq.) was added and the reaction mixture was allowed to warm to rt. Following pre-absorbtion onto silica, chromatography (ethyl acetate : light petroleum = 1 : 100 to 1 : 10) gave the title compound **10** (6.65 g, 84%), as a pale yellow oil, R_f = 0.42 (ethyl acetate : light petroleum = 1 : 9) (Found: M^+ + H,

392.2249. $C_{21}H_{34}NO_4Si$ requires *M*, 392.2257); ν_{max}/cm^{-1} 3409, 3067, 3034, 2954, 2830, 2885, 2857, 1721, 1500, 1390, 1258, 1108, 1064, 838 and 779; δ_H (300 MHz, $CDCl_3$) 0.00 (6 H, s, 2 × $SiCH_3$), 0.84 [9 H, s, $SiC(CH_3)_3$], 1.73–2.07 (6 H, m, 3 × CH_2), 2.97 (1 H, pent, *J* 9.7 Hz, 2-CH), 3.95 and 4.05 (each 1 H, d, *J* 10.0 Hz, 3-H), 5.09 (2 H, s, $PhCH_2$), 5.45 (1 H, br. s, NH), 7.36 (5 H, s, ArH) and 9.61 (1 H, s, CHO); δ_C (75 MHz, $CDCl_3$) −5.8 (2), 18.0, 18.3, 23.0, 23.7, 25.6, 37.2, 61.2, 66.7, 67.3, 128.1(2), 128.4, 136.1, 155.4 and 200.4; *m*/*z* (CI^+) 392 (M^+ + 1, 100%).

(4*SR*,5*RS*)-4-(*tert*-Butyldimethylsilyloxymethyl)-4-cyclobutyl-5-propen-2-yl-1,3-oxazolidin-2-one (25). Propen-2-ylmagnesium bromide (0.5 M in toluene, 297 mL, 148.5 mmol, 3.75 eq.) was added over 1 h to the aldehyde **10** (15.5 g, 39.6 mmol) in THF (800 mL) at −78 °C, and the reaction mixture stirred at −78 °C for 2 h then allowed to warm to rt overnight. The reaction mixture was stirred for another 36 h at rt before saturated aqueous ammonium chloride (500 mL) was added. The aqueous phase was extracted with ether (3 × 500 mL) and the organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography (ethyl acetate : light petroleum = 1 : 10) of the residue gave the title compound **25** (8.5 g, 66%) as a single diastereoisomer, R_f = 0.30 (ethyl acetate : light petroleum = 1 : 4) as a white solid, m.p. 110–112 °C (Found: C, 62.76; H, 9.62; N, 4.20%. $C_{17}H_{31}NO_3Si$ requires C, 62.73; H, 9.60; N, 4.30; Found: M^+ + H, 326.2150, $C_{17}H_{32}NO_3Si$ requires *M*, 326.2152); ν_{max}/cm^{-1} 3240, 3137, 2952, 2935, 2892, 2859, 1756, 1465, 1384, 1344, 1254, 1106, 903, 840 and 777; δ_H (400 MHz, $CDCl_3$) 0.02 (6 H, s, 2 × $SiCH_3$), 0.87 [9 H, s, $SiC(CH_3)_3$], 1.69–2.18 (6 H, m, 3 × CH_2), 1.80 (3 H, s, 3′-H_3), 2.70 (1 H, pent, *J* 8.2 Hz, 4-CH), 3.43 (2 H, s, 4-CH_2), 4.50 (1 H, s, 5-H), 5.04 and 5.13 (each 1 H, s, 1′-H) and 5.86 (1 H, s, NH); δ_C (100 MHz, $CDCl_3$) −5.9, −5.8, 17.4, 18.1, 19.9, 22.4, 24.3, 25.7, 39.4, 63.9, 65.0, 82.2, 113.9, 138.0 and 158.9; *m*/*z* (CI^+) 343 (M^+ + 18, 75%) and 326 (M^+ + 1, 100).

(4*SR*,5*SR*)-4-(*tert*-Butyldimethylsilyloxymethyl)-4-cyclobutyl-5-(2-methyloxiran-2-yl)-1,3-oxazolidin-2-ones (29) and (30). *m*-Chloroperoxybenzoic acid (12.4 g, 50.25 mmol, 2.1 eq.) was added to the alkene **25** (7.79 g, 23.9 mmol) in DCM (95 mL) and the reaction mixture was stirred at rt for 18 h. Saturated aqueous sodium bicarbonate (75 mL) was added dropwise followed by saturated aqueous sodium sulfite (25 mL). Ether (100 mL) was added and the mixture stirred vigorously at rt for 1 h. The aqueous phase was extracted with ether (3 × 100 mL) and the organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography (ethyl acetate : light petroleum = 1 : 5 to 1 : 2) of the residue gave the title compounds **29** and **30** (6.15 g, 75%) as a colourless oil, a mixture of epimers, **29** : **30** = 77 : 23, R_f = 0.51 (ethyl acetate : light petroleum = 1 : 2) (Found: M^+ + H, 342.2103. $C_{17}H_{32}NO_4Si$ requires *M*, 342.2101); ν_{max}/cm^{-1} 3222, 3137, 2931, 2895, 2857, 1754, 1468, 1395, 1346, 1297, 1258, 1102, 1064, 1001, 952, 856, 838 and 778; *m*/*z* (CI^+) 359 (M^+ + 18, 50%) and 342 (M^+ + 1, 100). A sample of the major epimer **29** was isolated by crystallisation, m.p. 148–150 °C; δ_H (300 MHz, $CDCl_3$) major epimer **29** 0.07 (6 H, s, 2 × $SiCH_3$), 0.90 [9 H, s, $SiC(CH_3)_3$], 1.46 (3 H, s, 2′-CH_3), 1.74–2.08 (6 H, m, 3 × CH_2), 2.71 (1 H, m, 4-CH), 2.67 and 2.93 (each 1 H, d, *J* 4.7 Hz, 3′-H), 3.61 and 3.73 (each 1 H, d, *J* 10.5 Hz, 4-HC*H*), 4.07 (1 H, s, 5-H) and 6.01 (1 H, br. s, NH); δ_C (75 MHz, $CDCl_3$) −5.8, −5.7, 17.2, 18.2, 18.5, 22.4, 24.0, 25.8, 39.5, 52.8, 54.4, 63.5, 65.6, 80.1 and 158.4; minor epimer **30** 2.59 and 2.88 (each 1 H, d, *J* 4.7 Hz, 3′-H), 3.64 and 3.77 (each 1 H, d, *J* 10.2 Hz, 4-HC*H*), 4.01 (1 H, s, 5-H) and 6.09 (1 H, br. s, NH); δ_C (75 MHz, $CDCl_3$) 17.1, 18.0, 22.2, 23.8, 40.1, 50.3, 54.6, 63.2, 65.2 and 81.9.

(4*SR*,5*RS*)-4-(*tert*-Butyldimethylsilyloxymethyl)-4-cyclobutyl-5-(1-hydroxyprop-2-en-2-yl)-1,3-oxazolidin-2-one (31). *n*-Butyllithium (1.6 M in THF, 60.4 mL, 96.6 mmol, 5 eq.) was added to 2,2,6,6-tetramethylpiperidine (19.7 mL, 116 mmol, 6 eq.) in THF (85 mL) at 0 °C and the reaction mixture was allowed to warm to rt and was stirred at this temperature for 1 h. The reaction mixture was then added dropwise to the epoxides **29** and **30** (6.6 g, 19.3 mmol) in THF (190 mL) at 0 °C and the reaction mixture was allowed to warm to rt and was stirred for 3 h. Saturated aqueous ammonium chloride (150 mL) was added and the aqueous phase was extracted with ether (3 × 200 mL). The organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography (ethyl acetate : light petroleum = 1 : 10 to 1 : 2) of the residue gave the title compound **31** (4.43 g, 67%) as a white solid, R_f = 0.26 (ethyl acetate : light petroleum = 1 : 2), m.p. 157–158 °C (Found: C, 59.94; H, 9.35; N, 4.05%; $C_{17}H_{31}NO_4Si$ requires C, 59.79; H, 9.15; N, 4.10%. Found: M^+ + H, 342.2093. $C_{17}H_{32}NO_4Si$ requires *M*, 342.2101); ν_{max}/cm^{-1} 3258, 2952, 2933, 2891, 2859, 1751, 1467, 1389, 1355, 1255, 1106, 1031, 840 and 778; δ_H (400 MHz, $CDCl_3$) 0.05 (6 H, s, 2 × $SiCH_3$), 0.88 [9 H, s, $SiC(CH_3)_3$], 1.74–2.19 (6 H, m, 3 × CH_2), 2.38 (1 H, br. s, OH), 2.85 (1 H, pent *J* 8.5 Hz, 4-CH), 3.39 and 3.52 (each 1 H, d, *J* 10.2 Hz, 4-HC*H*), 4.19 (2 H, s, 1′-H_2), 4.79 (1 H, s, 5-H), 5.33 and 5.36 (each 1 H, s, 3′-H) and 6.28 (1 H, br. s, NH); δ_C (100 MHz, $CDCl_3$) −5.8(2), 17.1, 18.2, 22.0, 23.7, 25.7, 37.9, 63.2, 64.6, 65.6, 80.1, 114.6, 142.9 and 159.0; *m*/*z* (CI^+) 359 (M^+ + 18, 80%) and 342 (M^+ + 1, 100%).

(4*SR*,5*RS*)-3-Benzyl-4-(*tert*-butyldimethylsilyloxymethyl)-4-cyclobutyl-5-(1-hydroxyprop-2-en-2-yl)-1,3-oxazolidin-2-one (32). Sodium hydride (60% in mineral oil, 545 mg, 13.6 mmol, 1.05 eq.) and benzyl bromide (3.21 mL, 25.94 mmol, 2 eq.) were added successively to the alcohol **31** (4.43 g, 13.0 mmol) in THF (95 mL) and the reaction mixture was heated under reflux for 6 h. Saturated aqueous ammonium chloride (50 mL) was added and the aqueous phase was extracted with ether (3 × 75 mL). The organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography (ethyl acetate : light petroleum = 1 : 10 to 1 : 4) gave the benzyl ether **33** (348 mg, 5%), R_f = 0.50 (ethyl acetate : light petroleum = 1 : 4) (Found: M^+ + H, 522.3040. $C_{31}H_{44}NO_4Si$ requires *M*, 522.3040); ν_{max}/cm^{-1} 3086, 3063, 3031, 2951, 2932, 2890, 2858, 1751, 1496, 1465, 1402, 1356, 1255, 1099, 926, 841, 779 and 706; δ_H (300 MHz, $CDCl_3$) −0.08 and −0.03 (each 3 H, s, $SiCH_3$), 0.85 [9 H, s, $SiC(CH_3)_3$], 1.52–2.01 (6 H, m, 3 × CH_2), 2.86 (1 H, pent, *J* 8.7 Hz, 4-CH), 3.47 and 3.55 (each 1 H, d, *J* 11.0 Hz, 4-HC*H*), 4.05 and 4.18 (each 1 H, d, *J* 12.7 Hz, 1′-H), 4.36 (1 H, d, *J* 16.0 Hz, PhHC*H*N), 4.47 and 4.57 (each 1 H, d,

J 11.7 Hz, PhHC*H*O), 4.59 (1 H, d, *J* 16.0 Hz, PhHC*H*N), 5.05 (1 H, s, 5-H), 5.42 and 5.47 (each 1 H, s, 3′-H) and 7.22–7.40 (10 H, m, ArH); δ_C (75 MHz, $CDCl_3$) −6.0, −5.8, 17.0, 18.1, 22.7, 23.1, 25.7, 38.1, 45.8, 63.0, 68.3, 70.8, 72.4, 77.5, 117.2, 127.2, 127.5, 127.7, 127.8, 128.3, 128.4, 137.8, 138.6, 140.6 and 158.9; *m*/*z* (CI^+) 522 (M^+ + 1, 1%) and 91 (100). The second fraction was the title compound **32** (3.76 g, 64%), as a white solid, R_f = 0.31 (ethyl acetate : light petroleum = 1 : 2); m.p. 116–117 °C (Found: C, 66.93; H, 8.69; N, 3.19%; $C_{24}H_{37}NO_4Si$ requires C, 66.78; H, 8.64; N, 3.24%. Found: M^+ + H, 432.2567. $C_{24}H_{38}NO_4Si$ requires *M*, 432.2571); ν_{max}/cm^{-1} 3426, 3063, 3032, 2951, 2953, 2890, 2859, 1734, 1467, 1409, 1357, 1255, 1103, 1033, 919, 842 and 778; δ_H (400 MHz, $CDCl_3$) −0.05 and −0.02 (each 3 H, s, $SiCH_3$), 0.84 [9 H, s, $SiC(CH_3)_3$], 1.57–2.00 (6 H, m, 3 × CH_2), 2.35 (1 H, br. m, OH), 2.81 (1 H, pent, *J* 9.0 Hz, 4-CH), 3.46 and 3.49 (each 1 H, d, *J* 11.0 Hz, 4-HC*H*), 4.19 (1 H, dd, *J* 13.7, 6.5 Hz, 1′-H), 4.28 (1 H, dd, *J* 13.7, 4.7 Hz, 1′-H′), 4.38 and 4.57 (each 1 H, d, *J* 15.7 Hz, PhHC*H*), 5.07 (1 H, s, 5-H), 5.28 and 5.41 (each 1 H, s, 3′-H) and 7.23–7.36 (5 H, m, ArH); δ_C (100 MHz, $CDCl_3$) −6.0, −5.8, 17.1, 18.2, 22.8, 23.1, 25.8, 38.6, 45.8, 62.8, 63.9, 68.4, 78.0, 115.5, 127.4, 127.5, 128.5, 138.5, 144.1 and 158.8; *m*/*z* (CI^+) 449 (M^+ + 18, 1%), 432 (M^+ + 1, 10) and 91 (100). Starting material **31** (0.8 g, 18%) was also recovered.

(4*SR*,5*RS*)-3-Benzyl-4-(*tert*-butyldimethylsilyloxymethyl)-4-cyclobutyl-5-(1-methoxyprop-2-en-2-yl)-1,3-oxazolidin-2-one (34). Sodium hydride (132 mg, 3.29 mmol, 2 eq.) and MeI (1.05 mL, 16.4 mmol, 10 eq.) were added successively to the alcohol **32** (710 mg, 1.64 mmol) in THF (10 mL) and the reaction mixture was stirred at rt for 18 h before saturated aqueous ammonium chloride (10 mL) was added. The aqueous phase was extracted with ether (3 × 10 mL) and the organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography (ethyl acetate : light petroleum = 1 : 10) of the residue gave the title compound **34** (660 mg, 90%), R_f = 0.54 (ethyl acetate : light petroleum = 1 : 2) (Found: M^+, 445.2652. $C_{25}H_{39}NO_4Si$ requires *M*, 445.2648); ν_{max}/cm^{-1} 3063, 3031, 2951, 2932, 2892, 2859, 2822, 1752, 1467, 1403, 1356, 1255, 1103, 930, 841 and 778; δ_H (400 MHz, $CDCl_3$) −0.08 and −0.03 (each 3 H, s, $SiCH_3$), 0.84 [9 H, s, $SiC(CH_3)_3$], 1.55–1.99 (6 H, m, 3 × CH_2), 2.87 (1 H, pent, *J* 9.0 Hz, 4-CH), 3.32 (3 H, s, OCH_3), 3.46 and 3.51 (each 1 H, d, *J* 11.0 Hz, 4-HC*H*), 3.90 and 4.07 (each 1 H, d, *J* 13.0 Hz, 1′-H), 4.37 and 4.59 (each 1 H, d, *J* 15.7 Hz, PhHC*H*), 5.00 (1 H, s, 5-H), 5.37 and 5.40 (each 1 H, s, 3′-H) and 7.21–7.36 (5 H, m, ArH); δ_C (100 MHz, $CDCl_3$) −6.1, −5.9, 17.1, 18.1, 22.7, 23.1, 25.8, 38.1, 45.8, 58.1, 62.9, 68.2, 73.0, 77.5, 116.8, 127.1, 127.4, 128.3, 138.6, 140.5 and 158.8; *m*/*z* (EI^+) 445 (M^+, 1%) and 91 (100).

(4*SR*,5*RS*)-3-Benzyl-4-(*tert*-butyldimethylsilyloxymethyl)-4-cyclobutyl-5-[(*SR*)- and -(*RS*)-1-hydroxy-3-methoxyprop-2-yl]-1,3-oxazolidin-2-ones (35) and (36). Borane (1 M in THF, 8.2 mL, 8.22 mmol, 5 eq.) was added dropwise to the alkene **34** (660 mg, 1.48 mmol) in THF (5 mL) at 0 °C and the reaction mixture was stirred at this temperature for 18 h before ethanol (7.1 mL), saturated aqueous sodium acetate (23 mL) and hydrogen peroxide (30% in H_2O, 8 mL) were added. The reaction mixture was heated under reflux for 1 h then cooled. The aqueous phase was extracted with ether (3 × 35 mL) and the organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography (ethyl acetate : light petroleum = 1 : 4) of the residue gave the title compounds **35** and **36** (648 mg, 95%), as a mixture of diastereoisomers, **35** : **36** = 85 : 15, R_f = 0.21 (ethyl acetate : light petroleum = 1 : 2) (Found: M^+ + H, 464.2835. $C_{25}H_{42}NO_5Si$ requires *M*, 464.2833); ν_{max}/cm^{-1} 3443, 2930, 2892, 2859, 1732, 1468, 1409, 1357, 1297, 1255, 1169, 1104, 1036, 840 and 777; δ_H (400 MHz, $CDCl_3$) major epimer **35** 0.04 and 0.05 (each 3 H, s, $SiCH_3$), 0.88 [9 H, s, $SiC(CH_3)_3$], 1.50–2.05 (6 H, m, 3 × CH_2), 2.22 (1 H, br. s, OH), 2.37 (1 H, m, 2′-H), 2.57 (1 H, m, 4-CH), 3.36 (3 H, s, OCH_3), 3.57 and 3.63 (each 1 H, dd, *J* 6.0, 9.5 Hz, 3′-H), 3.66 (2 H, s, 4-CH_2), 3.85–3.94 (2 H, m, 1′-H_2), 4.17 (1 H, d, *J* 15.8 Hz, PhHC*H*), 4.48 (1 H, d, *J* 6.0 Hz, 5-H), 4.66 (1 H, d, *J* 15.8 Hz, PhHC*H*) and 7.24–7.40 (5 H, m, ArH); minor epimer **36** 0.03 and 0.05 (each 3 H, s, $SiCH_3$), 0.87 [9 H, s, $SiC(CH_3)_3$], 2.83 (1 H, br. t, *J* 5.5 Hz, OH), 3.36 (3 H, s, OCH_3), 3.72 (1 H, dd, *J* 9.5, 3.5 Hz, 3′-H), 3.79 (1 H, dd, *J* 9.5, 5.5 Hz, 3′-H′), 4.55 (1 H, d, *J* 7.8 Hz, 5-H) and 4.70 (1 H, d, *J* 15.7 Hz, PhHC*H*); δ_C (100 MHz, $CDCl_3$) major epimer **35** −5.9, −5.8, 17.2, 17.9, 23.1, 23.3, 25.7, 38.7, 40.8, 45.8, 59.1, 61.2, 62.3, 68.5, 73.3, 77.4, 127.3, 127.6, 128.5, 138.4 and 159.1; minor epimer **36** −5.8, 17.1, 17.9, 23.1, 23.4, 25.6, 38.7, 40.3, 45.8, 59.3, 60.8, 64.4, 68.8, 73.6, 75.4, 127.2, 127.6, 128.4, 138.5 and 159.5; *m*/*z* (CI^+) 464 (M^+ + 1, 1%) and 90 (100).

(4*SR*,5*RS*)-3-Benzyl-4-hydroxymethyl-4-cyclobutyl-5-(1-hydroxy-3-methoxyprop-2-yl)-1,3-oxazolidin-2-ones (9) and (37). Tetra-*n*-butylammonium fluoride (1 M in THF, 1.67 mL, 1.67 mmol, 1.2 eq.) was added to the mixture of the silyl ethers **35** and **36** (648 mg, 1.39 mmol) at 0 °C and the mixture allowed to warm to rt. After stirring for 1 h, brine (7 mL) was added and the aqueous layer was extracted with ether (3 × 15 mL). The organic extracts were dried ($MgSO_4$) and concentrated under reducd pressure. Chromatography (ethyl acetate : light petroleum = 1 : 2 to neat ethyl acetate) of the residue gave the title compounds **9** and **37** (328 mg, 67%) as a mixture of diastereoisomers, **9** : **37** = 85 : 15, R_f = 0.25 (EtOAc) (Found: M^+ + H, 350.1970. $C_{19}H_{28}NO_5$ requires *M*, 350.1968); ν_{max}/cm^{-1} 3418, 2938, 2894, 1722, 1432, 1415, 1357, 1253, 1093, 1070, 1036 and 765; δ_H (400 MHz, $CDCl_3$) major epimer **9** 1.58–2.05 (6 H, m, 3 × CH_2), 2.42 (1 H, m, 2′-H), 2.52–2.63 (2 H, m, 4-CH, OH), 3.36 (3 H, s, OCH_3), 3.47–3.57 (3 H, m, 3′-H_2, 4-HC*H*), 3.66 (1 H, d, *J* 13.0 Hz, 4-HC*H*), 3.82 (1 H, dd, *J* 4.0, 11.0 Hz, 1′-H), 3.96 (1 H, dd, *J* 5.5, 11.0 Hz, 1′-H′), 4.43 and 4.51 (each 1 H, d, *J* 15.7 Hz, PhHC*H*), 4.63 (1 H, d, *J* 4.5 Hz, 5-H) and 7.27–7.46 (5 H, m, ArH); minor epimer **37** 2.31 (1 H, br. s, OH), 3.73 (2 H, m, 1′-H_2), 4.44 and 4.56 (each 1 H, d, *J* 15.7 Hz, PhHC*H*) and 4.68 (1 H, d, *J* 6.2 Hz, 5-H); δ_C (100 MHz, $CDCl_3$) major epimer **9** 17.5, 22.8, 23.0, 39.0, 41.0, 45.3, 59.1, 60.7, 61.5, 68.6, 73.5, 77.3, 127.8(2), 128.9, 138.3 and 159.0; minor epimer **37**23.1, 39.1, 40.5, 59.2, 60.7, 64.2, 68.5, 72.5, 75.8, 138.4 and 159.0; *m*/*z* (CI^+) 350 (M^+ + 1, 5%) and 91 (100).

(1*RS*,6*SR*)-4,7-Bis-benzyl-6-cyclobutyl-2-methoxymethyl-4,7-diaza-9-oxabicyclo[4.3.0]nonan-8-ones (39) and (40). Freshly

distilled methane sulfonyl chloride (0.112 mL, 1.42 mmol, 3 eq.) and Et_3N (0.20 mL, 1.42 mmol, 3 eq.) were added successively to a mixture of the diols **9** and **37** (166 mg, 0.475 mmol) in DCM (5 mL) at 0 °C. The reaction mixture was allowed to warm to rt and was stirred for 1 h before the addition of ether (5 mL) and saturated aqueous ammonium chloride (10 mL). The aqueous phase was extracted with ether (3 × 10 mL) and the organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure to leave a mixture of the bis-mesylates **38** (228 mg) that was used without purification.

The bis-mesylates **38** (228 mg) were dissolved in benzylamine (15 mL) and the solution heated at 80 °C for 18 h. After cooling to rt, the benzylamine was removed by distillation under reduced pressure. Chromatography (ethyl acetate : light petroleum = 1 : 20 to 1 : 10) of the residue achieved partial separation of the piperidines **39** and **40** to give the title compound **39** (72 mg, 36%), R_f = 0.28 (ethyl acetate : light petroleum = 1 : 2) (Found: M^+, 420.2410. $C_{26}H_{32}N_2O_3$ requires *M*, 420.2413); ν_{max}/cm^{-1} 3083, 3060, 3029, 2924, 2872, 2811, 1744, 1494, 1453, 1405, 1349, 1294, 1201, 1168, 1117, 1090, 1060, 1028, 978, 818 and 746; δ_H (400 MHz, $CDCl_3$) 1.40–1.78 (5 H, m, cyclobutyl H), 2.00 (1 H, m, cyclobutyl H), 2.10 (1 H, d, *J* 12.5 Hz, 5-H), 2.22 (1 H, m, 2-H), 2.36 (1 H, t, *J* 10.5 Hz, 3-H), 2.41 (1 H, d, *J* 12.5 Hz, 5-H′), 2.49 (1 H, pent, *J* 8.7 Hz, 6-CH), 2.58 (1 H, dd, *J* 7.25, 10.5 Hz, 3-H′), 3.32–3.37 (6 H, m, 2-CH, OCH_3, $PhCH_2$), 3.57 (1 H, t, *J* 8.5 Hz, 2-CH′), 3.91 and 4.28 (each 1 H, d, *J* 16.0 Hz, PhHC*H*), 4.51 (1 H, d, *J* 2.5 Hz, 1-H) and 7.21–7.34 (10 H, m, ArH); δ_C (100 MHz, $CDCl_3$) 17.6, 22.9, 23.3, 36.7, 39.2, 44.7, 50.6, 53.0, 59.1, 61.9, 64.4, 72.0, 74.3, 127.2, 127.3, 127.9, 128.3(2), 128.9, 138.0, 138.3 and 159.1; *m*/*z* (EI) 420 (M^+, 1%) and 91 (100). The second fraction was a mixture of the title compounds **39** and **40** (53 mg, 26%), **39** : **40** = 56 : 44, R_f = 0.28–0.22 (ethyl acetate : light petroleum = 1 : 2) (Found: M^+, 420.2412. $C_{26}H_{32}N_2O_3$ requires *M*, 420.2413); ν_{max}/cm^{-1} 3083, 3061, 3029, 2927, 2869, 2823, 1746, 1495, 1453, 1436, 1403, 1355, 1334, 1193, 1170, 1106, 1053, 1027, 996, 923, 809 and 743; δ_H (400 MHz, $CDCl_3$) minor epimer **40** 2.75–2.85 (2 H, m, 3-H, 5-H), 3.24 (1 H, d, *J* 12.8 Hz, PhHC*H*), 3.47 (1 H, dd, *J* 3.0, 9.5 Hz, 2-CH), 3.53 (1 H, dd, *J* 5.25, 9.5 Hz, 2-CH′), 4.02 (1 H, d, *J* 15.5 Hz, PhHC*H*), 4.40 (1 H, d, *J* 8.7 Hz, 1-H) and 4.45 (1 H, d, *J* 15.5 Hz, PhHC*H*); δ_C (100 MHz, $CDCl_3$) minor epimer **40**16.9, 23.3, 23.7, 41.2, 41.6, 44.4, 53.3(2), 59.1, 62.4, 63.6, 71.8, 73.8, 127.4(2), 128.0, 128.3, 128.4, 129.3, 137.9, 138.1 and 158.4; *m*/*z* (CI^+) 421 (M^+ + 1, 100%).

(1*RS*,2*SR*,6*SR*)-7-Benzyl-6-cyclobutyl-2-methoxymethyl-4,7-diaza-9-oxabicyclo[4.3.0]nonan-8-one (8). A solution of formic acid (93 μL, 0.025 mmol, 0.4 eq.) in MeOH (1 mL) was added to the *N*-benzylpiperidine **39** (26 mg, 0.062 mmol) and 10% Pd/C (41 mg) under N_2 and the reaction mixture was stirred at rt for 20 min. Potassium carbonate (50 mg) was added, the reaction mixture was filtered through celite and the residue was washed with ether. After concentration under reduced pressure, chromatography (MeOH : ether = 1 : 50, saturated in ammonia) of the residue gave the title compound **8** (14 mg, 71%), R_f = 0.38 (MeOH : ether = 1 : 10 saturated in ammonia) (Found: M^+, 330.1941. $C_{19}H_{26}N_2O_3$ requires *M*, 330.1943); ν_{max}/cm^{-1} 3343, 3086, 3062, 3029, 2935, 2871, 2832, 2815, 1742, 1672, 1496, 1454, 1432, 1409, 1345, 1199, 1167, 1146, 1112, 1090, 1071, 984, 759 and 707; δ_H (400 MHz, $CDCl_3$) 1.54–2.00 (7 H, m, 3 × CH_2, 6-CH), 2.12 (1 H, m, 2-H), 2.37 (1 H, d, *J* 14.2 Hz, 5-H), 2.57 (1 H, t, *J* 12.0 Hz, 3-H), 2.61 (1 H, d, *J* 14.2 Hz, 5-H′), 2.91 (1 H, dd, *J* 6.5, 12.0 Hz, 3-H′), 3.31 (1 H, dd, *J* 6.0, 9.0 Hz, 2-CH), 3.36 (3 H, s, CH_3), 3.52 (1 H, t, *J* 9.0 Hz, 2-CH′), 4.22 and 4.43 (each 1 H, d, *J* 15.7 Hz, PhHC*H*), 4.71 (1 H, d, *J* 2.7 Hz 1-H) and 7.24–7.39 (5 H, m, ArH); δ_C (100 MHz, $CDCl_3$) 17.5, 22.2, 22.8, 35.8, 38.5, 40.7, 44.6, 45.0, 59.0, 63.4, 71.4, 73.6, 127.8, 127.8, 128.7, 138.1 and 158.7; *m*/*z* (CI^+) 331 (M^+ + 1, 60%) and 91 (100).

(1*RS*,2*SR*,6*SR*)-4,7-Bis-benzyl-6-cyclobutyl-2-hydroxymethyl-4,7-diaza-9-oxabicyclo[4.3.0]nonan-8-one (41). Boron tribromide in THF (1 M in THF, 0.415 mL, 415 mmol, 0.8 eq.) was added dropwise to the methyl ether **39** (209 mg, 0.497 mmol) in DCM (7 mL) at 0 °C and the reaction mixture was stirred at 0 °C for 4 h. Saturated aqueous sodium bicarbonate (0.5 mL) was added very slowly over 10 min, the reaction mixture was stirred at rt for 30 min and a second portion of a saturated aqueous sodium bicarbonate (1 mL) was added. The aqueous phase was extracted with ether (3 × 5 mL) and the organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography (ethyl acetate : light petroleum = 1 : 4 to 1 : 2) of the residue gave the title compound **41** (124 mg, 61%), R_f = 0.15 (ethyl acetate : light petroleum = 1 : 1) (Found: M^+ + H, 407.2339. $C_{25}H_{31}N_2O_3$ requires *M*, 407.2335); ν_{max}/cm^{-1} 3422, 3030, 2942, 2872, 2815, 1727, 1495, 1413, 1355, 1169, 1061, 1032, 977, 817 and 745; δ_H (400 MHz, $CDCl_3$) 1.41–1.81 (5 H, m, cyclobutyl H), 2.00 (1 H, m, cyclobutyl H), 2.10 (1 H, d, *J* 12.2 Hz, 5-H), 2.18 (1 H, m, 2-H), 2.40 (1 H, d, *J* 10.5 Hz, 3-H), 2.42 (1 H, d, *J* 12.2 Hz, 5-H′), 2.52 (1 H, pent, *J* 8.5 Hz, 6-CH), 2.59 (1 H, dd, *J* 7.2, 10.5 Hz, 3-H′), 3.32 and 3.36 (each 1 H, d, *J* 13.0 Hz, PhHC*H*), 3.70 (1 H, dd, *J* 5.7, 10.7 Hz, 2-CH), 3.83 (1 H, dd, *J* 7.7, 10.7 Hz, 2-CH′), 3.94 and 4.28 (each 1 H, d, *J* 16.0 Hz, PhHC*H*), 4.57 (1 H, d, *J* 3.0 Hz, 1-H) and 7.21–7.35 (10 H, m, ArH); δ_C (100 MHz, $CDCl_3$) 17.6, 23.0, 23.3, 38.4, 39.3, 44.7, 50.4, 53.4, 62.0, 62.3, 64.5, 74.7, 127.2, 127.4, 127.9, 128.3, 128.4, 128.9, 137.9, 138.2 and 159.0; *m*/*z* (EI^+) 406 (M^+, 1%) and 91 (100).

(4*SR*,5*RS*)-3-Benzyl-4-(*tert*-butyldimethylsilyloxymethyl)-4-cyclobutyl-5-(1-bromoprop-2-en-2-yl)-1,3-oxazolidin-2-one (43). Carbon tetrabromide (1.16 g, 3.48 mmol, 1.5 eq.) was added to the alcohol **32** (1 g, 2.32 mmol) and triphenylphosphine (1.22 g, 4.64 mmol, 2 eq.) in MeCN (26 mL) at 0 °C and the reaction mixture was warmed to rt then stirred for 2 h. After concentration under reduced pressure and pre-absorbtion of the residue onto the silica, chromatography (ethyl acetate : light petroleum = 1 : 25 to 1 : 10) gave the title compound **43** (1.15 g, 100%) as a colourless oil, R_f = 0.15 (ethyl acetate : light petroleum = 1 : 10) (Found: M^+ + H, 494.1719. $C_{24}H_{37}NO_3{}^{79}BrSi$ requires *M*, 494.1727); ν_{max}/cm^{-1} 3088, 3063, 3032, 2952, 2932, 2897, 2859, 1752, 1496, 1468, 1402, 1355, 1294, 1255, 1211, 1164, 1102, 1031, 1006, 930, 840 and 779; δ_H (300 MHz, $CDCl_3$) −0.03 and 0.00 (each 3 H, s, $SiCH_3$), 0.86 [9 H, s, $SiC(CH_3)_3$], 1.61–2.10 (6 H, m, 3 × CH_2), 2.82 (1 H, pent, *J* 9.0 Hz, 4-CH),

3.45 (2 H, s, 4-CH_2), 4.09 and 4.15 (each 1 H, d, *J* 11.2 Hz, 1′-H), 4.44 and 4.54 (each 1 H, d, *J* 15.7 Hz, PhHC*H*), 5.14 (1 H, s, 5-H), 5.54 and 5.62 (each 1 H, s, 3′-H) and 7.29–7.39 (5 H, m, ArH); δ_C (75 MHz, $CDCl_3$) −6.0, −5.8, 17.3, 18.1, 23.0, 23.6, 25.8, 32.9, 39.1, 45.9, 63.0, 68.5, 77.2, 119.8, 127.4, 127.5, 128.5, 138.4, 140.2 and 158.5; *m*/*z* (CI^+) 513 (M^+ + 18, 25%), 511 (M^+ + 18, 25), 496 (M^+ + 1, 5) and 494 (M^+ + 1, 5) and 106 (100).

(4*SR*,5*RS*)-3-Benzyl-4-(*tert*-butyldimethylsilyloxymethyl)-4-cyclobutyl-5-[1-(2-phenylethoxy)prop-2-en-2-yl]-1,3-oxazolidin-2-one (44). Sodium hydride (60% in mineral oil, 176 mg, 4.40 mmol, 2 eq.) was added to 2-phenylethanol (0.26 mL, 2.18 mmol, 0.99 eq.) in THF (15 mL) at 0 °C and the suspension stirred at rt for 30 min. The bromide **43** (1.09 g, 2.20 mmol) in THF (10 mL) was added and the reaction mixture stirred for 3 h. Saturated aqueous ammonium chloride (15 mL) was added and the aqueous phase was extracted with ether (3 × 20 mL). The organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography (ethyl acetate : light petroleum = 1 : 25) of the residue gave the title compound **44** (1.17 g, 99%) as a colourless oil, R_f = 0.56 (ethyl acetate : light petroleum = 1 : 4) (Found: M^+ + H, 536.3189. $C_{32}H_{46}NO_4Si$ requires *M*, 536.3191); ν_{max}/cm^{-1} 3063, 3029, 2950, 2928, 2858, 1752, 1603, 1496, 1467, 1404, 1355, 1255, 1101, 929, 841 and 779; δ_H (300 MHz, $CDCl_3$) −0.07 and −0.02 (each 3 H, s, $SiCH_3$), 0.86 [9 H, s, $SiC(CH_3)_3$], 1.51–1.92 (6 H, m, 3 × CH_2), 2.82 (1 H, pent, *J* 8.7 Hz, 4-CH), 2.91 (2 H, t, *J* 7.0 Hz, 2″-H_2), 3.45 and 3.51 (each 1 H, d, *J* 10.7 Hz, 4-HC*H*), 3.62 (1 H, dt, *J* 9.2, 7.0 Hz, 1″-H), 3.71 (1 H, dt, *J* 9.2, 7.2 Hz, 1″-H′), 3.99 and 4.14 (each 1 H, d, *J* 13.0 Hz, 1′-H), 4.37 and 4.60 (each 1 H, d, *J* 15.7 Hz, PhHC*H*), 4.94 (1 H, s, 5-H), 5.38 (2 H, s, 3′-H_2) and 7.21–7.39 (10 H, m, ArH); δ_C (75 MHz, $CDCl_3$) −6.0, −5.8, 17.1, 18.1, 22.8, 23.1, 25.8, 36.3, 38.2, 45.8, 62.9, 68.3, 71.2, 71.5, 77.2, 116.9, 126.2, 127.2, 127.5, 128.4(2), 128.9, 138.7, 138.8, 140.6 and 158.9; *m*/*z* (CI^+) 536 (M^+ + 1, 5%) and 309 (100).

(4*SR*,5*RS*)-3-Benzyl-4-(*tert*-butyldimethylsilyloxymethyl)-4-cyclobutyl-5-[(*SR*)-1-hydroxy-3-(2-phenylethoxy)prop-2-yl]-1,3-oxazolidin-2-one (45). Borane (1 M in THF, 21.8 mL, 21.8 mmol, 10 eq.) was added dropwise to the alkene **44** (1.17 g, 2.18 mmol) in THF (21 mL) at −20 °C and the reaction mixture was warmed to 0 °C then stirred for 18 h. Ethanol (19 mL), saturated aqueous sodium acetate (61 mL) and hydrogen peroxide (30% in water, 22 mL) were added dropwise in that order and the reaction mixture was heated under reflux for 2.5 h. After cooling the aqueous phase was extracted with ether (3 × 150 mL), and the organic extracts were dried ($MgSO_4$) then concentrated under reduced pressure. Chromatography (ethyl acetate : light petroleum = 1 : 10 to 1 : 4) of the residue gave the alcohol **45** (870 mg, 72%) as a 3 : 1 mixture of 2′-epimers. Further chromatography (ethyl acetate : light petroleum = 1 : 4) gave the title compound **45** (566 mg, 47%), R_f = 0.26 (ethyl acetate : light petroleum = 1 : 2) (Found: M^+ + NH_4, 571.3569. $C_{32}H_{51}N_2O_5Si$ requires *M*, 571.3562); ν_{max}/cm^{-1} 3442, 3063, 3029, 2969, 2953, 2860, 1733, 1604, 1496, 1468, 1409, 1357, 1297, 1255, 1206, 1171, 1106, 1032, 980, 841 and 778; δ_H (300 MHz, $CDCl_3$) 0.06 and 0.08 (each 3 H, s, $SiCH_3$), 0.91 [9 H, s, $SiC(CH_3)_3$], 1.35–1.94 (6 H, m, 3 × CH_2), 2.19 (1 H, br. s, OH), 2.38 (1 H, m, 2′-H), 2.54 (1 H, pent, *J* 8.7 Hz, 4-CH), 2.91 (2 H, t, *J* 6.7 Hz, 2″-H_2), 3.62–3.75 (6 H, m, 4-CH_2, 1′-H_2, 1″-H_2), 3.91 (2 H, d, *J* 4.5 Hz, 3′-H_2), 4.18 (1 H, d, *J* 16.0 Hz, PhHC*H*), 4.49 (1 H, d, *J* 6.2 Hz, 5-H), 4.69 (1 H, d, *J* 16.0 Hz, PhHC*H*) and 7.22–7.42 (10 H, m, ArH); δ_C (75 MHz, $CDCl_3$) −5.9, −5.8, 17.2, 17.9, 23.0, 23.2, 25.6, 36.2, 38.6, 40.8, 45.7, 61.1, 62.2, 68.5, 71.5, 72.2, 77.3, 126.3, 127.2, 127.5, 128.4(2), 128.7, 138.4, 138.7 and 159.2; *m*/*z* (CI^+) 571 (M^+ + 18, 2%), 554 (M^+ + 1, 3) and 102 (100).

(4*SR*,5*RS*)-3-Benzyl-4-cyclobutyl-4-hydroxymethyl-5-[(*SR*)-1-hydroxy-3-(2-phenylethoxy)prop-2-yl]-1,3-oxazolidin-2-one (46). Tetra-*n*-butylammonium fluoride in THF (1 M in THF, 1.23 mL, 1.23 mmol, 1.2 eq.) was added to the silyl ether **45** (566 mg, 1.02 mmol) in THF (10 mL) at 0 °C and the reaction mixture was warmed to rt then stirred for 30 min. After concentration under reduced pressure and pre-absorbtion onto silica, chromatography (ethyl acetate : light petroleum = 1 : 2 to neat ethyl acetate) of the residue gave the title compound **46** (313 mg, 70%), R_f = 0.16 (ethyl acetate : light petroleum = 3 : 2) (Found: M^+ + H, 440.2435. $C_{26}H_{34}NO_5$ requires *M*, 440.2431); ν_{max}/cm^{-1} 3396, 3062, 3029, 2942, 2870, 1723, 1604, 1495, 1432, 1415, 1357, 1297, 1253, 1202, 1167, 1110, 1031, 975 and 911; δ_H (400 MHz, $CDCl_3$) 1.45–1.90 (6 H, m, 3 × CH_2), 2.34–2.50 (2 H, m, 4-CH, 2′-H), 2.88 (4 H, m, 2″-H_2, 2 × OH), 3.55 (3 H, m, 4-HC*H*, 1′-H, 1″-H), 3.64–3.74 (4 H, m, 4-HC*H*, 1′-H′, 1″-H′, 3′-H), 3.93 (1 H, dd, *J* 5.75, 11.0 Hz, 3′-H′), 4.35 and 4.55 (each 1 H, d, *J* 16.0 Hz, PhHC*H*), 4.59 (1 H, d, *J* 4.2 Hz, 5-H) and 7.19–7.42 (10 H, m, ArH); δ_C (100 MHz, $CDCl_3$) 17.4, 22.8, 22.9, 36.1, 39.0, 41.0, 45.3, 60.3, 61.1, 68.8, 71.5, 72.2, 77.4, 126.3, 127.6, 127.8, 128.4, 128.7(2), 138.3, 138.6 and 159.4; *m*/*z* (CI^+) 457 (M^+ + 18, 3%), 440 (M^+ + 1, 10) and 102 (100).

(1*RS*,2*SR*,6*SR*)-4,7-Bis-benzyl-6-cyclobutyl-2-(2-phenylethoxy)methyl-4,7-diaza-9-oxabicyclo[4.3.0]nonan-8-one (48). Freshly distilled methane sulfonyl chloride (0.152 mL, 1.96 mmol, 4 eq.) and Et_3N (0.341 mL, 2.44 mmol, 5 eq.) were added successively to the diol **46** (215 mg, 0.489 mmol) in DCM (10 mL) at 0 °C and the reaction mixture was allowed to warm to rt then stirred for 1 h. Saturated aqueous ammonium chloride (10 mL) and ether (15 mL) were added and the aqueous phase was extracted with ether (3 × 20 mL). The organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure to give the bis-mesylate **47**, R_f = 0.51 (ethyl acetate : light petroleum = 3 : 2).

The bis-mesylate **47** (140 mg) was dissolved in benzylamine (12 mL) and heated at 95 °C for 15 h. After cooling to rt, unreacted benzylamine was removed by distillation under reduced pressure. The residue was dissolved in ether (12 mL) and saturated aqueous potassium carbonate (10 mL) was added. The mixture was stirred vigorously at rt for 30 min and then the organic and aqueous phases were separated. The aqueous phase was extracted with ether (3 × 15 mL) and the organic extracts were dried ($MgSO_4$) then concentrated under reduced pressure. Chromatography (ethyl acetate : light petroleum = 1 : 10 to 1 : 4) of the residue gave the title compound

48 (92 mg, 37%), R_f = 0.25 (ethyl acetate : light petroleum = 1 : 4) (Found: M^+ + H, 511.2966. $C_{33}H_{39}N_2O_3$ requires *M*, 511.2955); ν_{max}/cm^{-1} 3086, 3062, 3028, 2942, 2866, 2808, 1746, 1603, 1495, 1454, 1406, 1361, 1171, 1113, 1095, 1064, 1028, 983, 913, 818 and 748; δ_H (300 MHz, $CDCl_3$) 1.36–2.00 (6 H, m, 3 × CH_2), 2.09 (1 H, d, *J* 12.5 Hz, 5-H), 2.21 (1 H, m, 2-H), 2.37 (1 H, t, *J* 10.5 Hz, 3-H), 2.40 (1 H, d, *J* 12.5 Hz, 5-H′), 2.47 (1 H, pent, *J* 9.0 Hz, 6-CH), 2.54 (1 H, dd, *J* 10.5, 7.2 Hz, 3-H′), 2.88 (2 H, t, *J* 7.0 Hz, 2′-H_2), 3.32 (2 H, s, $PhCH_2$), 3.41 (1 H, dd, *J* 9.2, 6.5 Hz, 2-CH), 3.59–3.73 (3 H, m, 1′-H_2, 2-CH′), 3.90 and 4.28 (each 1 H, d, *J* 15.7 Hz, PhHC*H*), 4.46 (1 H, d, *J* 2.5 Hz, 1-H) and 7.20–7.36 (15 H, m, ArH); δ_C (75 MHz, $CDCl_3$) 17.6, 22.9, 23.2, 36.2, 36.8, 39.2, 44.7, 50.6, 52.9, 61.9, 64.4, 70.0, 72.1, 74.3, 126.2, 127.2, 127.3, 127.9, 128.3(3), 128.9, 138.0, 138.3, 138.9 and 159.1; *m*/*z* (EI^+) 510 (M^+, 1%) and 91 (100).

(1*RS*,2*SR*,6*SR*)-7-Benzyl-6-cyclobutyl-2-(2-phenylethoxy)methyl-4,7-diaza-9-oxabicyclo[4.3.0]nonan-8-one (49). Following the procedure outlined for the preparation of piperidine **8**, the benzylamine **48** (105 mg, 0.206 mmol), after chromatography (ethyl acetate : light petroleum = 3 : 2 with 2% triethylamine to neat ethyl acetate) gave the title compound **49** (53 mg, 61%), R_f = 0.24 (1% methanol in ethyl acetate) (Found: M^+ + H, 421.2486. $C_{26}H_{33}N_2O_3$ requires *M*, 421.2486); ν_{max}/cm^{-1} 3348, 3062, 3028, 2938, 2865, 1743, 1603, 1496, 1410, 1259, 1093, 811 and 755; δ_H (400 MHz, C_6D_6) 1.25–1.60 (5 H, m, cyclobutyl H), 1.74 (1 H, m, cyclobutyl H), 1.95 (1 H, m, 2-H), 2.19 (1 H, d, *J* 13.6 Hz, 5-H), 2.2 (1 H, pent, *J* 8.5 Hz, 6-CH), 2.35 (1 H, d, *J* 13.6 Hz, 5-H′), 2.44 (1 H, t, *J* 11.7 Hz, 3-H), 2.73 (1 H, dd, *J* 6.4, 11.5 Hz, 3-H′), 2.82 (2 H, t, *J* 6.9 Hz, 2′-H_2), 3.18 (1 H, dd, *J* 6.2, 9.0 Hz, 2-CH), 3.45–3.59 (3 H, m, 2-CH′, 1′-H_2), 4.17 and 4.24 (each 1 H, d, *J* 15.6 Hz, PhHC*H*), 4.54, (1 H, d, *J* 2.7 Hz, 1-H), 7.08–7.26 (8 H, m, ArH) and 7.41 (2 H, d, *J* 7.0 Hz, ArH); δ_C (100 MHz, C_6D_6) 17.5, 22.4, 22.8, 36.3, 36.4, 38.8, 41.4, 44.5, 45.9, 62.8, 69.7, 71.9, 73.5, 126.1, 127.3, 128.0, 128.3, 128.4, 129.0, 139.2(2) and 158.4; *m*/*z* (ES^+) 421 (M^+ + 1, 100%).

(4*SR*,5*RS*)-3-Benzyl-4-(*tert*-butyldimethylsilyloxymethyl)-5-(1-*tert*-butyldimethylsilyloxyprop-2-en-2-yl)-4-cyclobutyl-1,3-oxazolidin-2-one (50) and (4*SR*,5*RS*)-3-Benzyl-4-cyclobutyl-4-hydroxymethyl-5-(1-hydroxyprop-2-en-2-yl)-1,3-oxazolidin-2-one (51). Sodium hydride (60% in mineral oil, 195 mg, 4.87 mmol, 2 eq.) was added to the alcohol **32** (1.05 g, 2.43 mmol) in THF (15 mL) and the suspension stired for 30 min. 2-Phenylethyl bromide (0.366 mL, 2.68 mmol, 1.1 eq.) in THF (5 mL) was added and the reaction mixture was stirred for 15 h. After adding saturated aqueous NH_4Cl (15 mL), the aqueous phase was extracted with ether (3 × 20 mL) and the organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure. Chromatography of the residue (ethyl acetate : light petroleum = 1 : 10 to 3 : 2) gave the title compound **50** (501 mg, 38%), R_f = 0.59 (ethyl acetate : light petroleum = 1 : 4) (Found: M^+ + H, 546.3430. $C_{30}H_{52}NO_4Si_2$ requires *M*, 546.3435); ν_{max}/cm^{-1} 3088, 3064, 3031, 2953, 2932, 2889, 2858, 1755, 1496, 1467, 1404, 1357, 1291, 1255, 1106, 1005, 934, 917, 840 and 778; δ_H (300 MHz, $CDCl_3$) −0.04, 0.01, 0.09 and 0.10 (each 3 H, s, $SiCH_3$), 0.88 and 0.94 [each 9 H, s, $SiC(CH_3)_3$], 1.53–2.03 (6 H, m, 3 × CH_2), 2.91 (1 H, pent, *J* 8.5 Hz, 4-CH), 3.49 and 3.55 (each 1 H, d, *J* 11.0 Hz, 4-*H*CH), 4.26 (2 H, s 1′-H_2), 4.36 and 4.65 (each 1 H, d, *J* 15.7 Hz, Ph*H*CH), 5.06 (1 H, s, 5-H), 5.28 and 5.44 (each 1 H, s, 3′-H) and 7.23–7.40 (5 H, m, ArH); δ_C (75 MHz, $CDCl_3$) −6.1, −5.9, −5.5(2), 16.9, 18.0, 18.2, 22.6, 23.0, 25.7, 37.8, 45.8, 62.6, 63.4, 68.1, 77.8, 114.2, 127.1, 127.4, 128.3, 138.6, 143.0 and 158.9; *m*/*z* (CI) 546 (M^+ + 1, 20%) and 106 (100). The second fraction was the title compound **51** (333 mg, 43%), R_f = 0.26 (ethyl acetate : light petroleum = 3 : 2) (Found: M^+ + H, 318.1708. $C_{18}H_{24}NO_4$ requires *M*, 318.1705); ν_{max}/cm^{-1} 3409, 3064, 3032, 2942, 2871, 1725, 1496, 1432, 1414, 1357, 1293, 1254, 1202, 1158, 1068, 1025, 979, 917 and 817; δ_H (300 MHz, $CDCl_3$) 1.54–1.97 (6 H, m, 3 × CH_2), 2.58 (1 H, pent, *J* 8.7 Hz, 4-CH), 3.55 and 3.62 (each 1 H, d, *J* 12.5 Hz, 4-*H*CH), 4.06 (2 H, br. s, OH), 4.18 (1 H, d, *J* 13.0 Hz, 1′-H), 4.34 (1 H, d, *J* 16.0 Hz, Ph*H*CH), 4.38 (1 H, d, *J* 13.0 Hz, 1′-H′), 4.68 (1 H, d, *J* 16.0 Hz, PhHC*H*), 5.11 (1 H, s, 5-H), 5.23 and 5.48 (each 1 H, s, 3′-H) and 7.27–7.44 (5 H, m, ArH); δ_C (75 MHz, $CDCl_3$) 17.2, 22.8, 22.9, 39.5, 45.8, 60.2, 63.2, 69.7, 78.9, 116.7, 127.5, 127.7, 128.6, 138.2, 144.2 and 159.4; *m*/*z* (CI) 335 (M^+ + 18, 15%) , 318 (M^+ + 1, 15) and 88 (100).

(1*RS*,6*SR*)-4,7-Bis-benzyl-6-cyclobutyl-2-methylene-4,7-diaza-9-oxabicyclo[4.3.0]nonan-8-one (53). Methane sulfonyl chloride (0.338 mL, 4.36 mmol, 4 eq.) and Et_3N (0.761 mL, 5.45 mmol, 5 eq.) were added to the diol **51** (346 mg, 1.09 mmol) in DCM (10 mL) at 0 °C and the reaction mixture stirred at rt for 1 h before the addition of saturated aqueous NH_4Cl (10 mL) followed by ether (15 mL). The aqueous phase was extracted with ether (3 × 20 cm^3) and the organic layer extracts were dried ($MgSO_4$) then concentrated under reduced pressure to give the bis-mesylate **52**.

This bis-mesylate **52** was dissolved in benzylamine (12 mL) and the solution heated at 95 °C for 18 h then allowed to cool to rt and concentrated under reduced pressure. The residue was dissolved in ether (12 mL), saturated aqueous K_2CO_3 (10 mL) was added and the mixture was stirred vigorously at rt for 30 min. The aqueous phase was extracted with ether (3 × 15 mL) and the organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue (ethyl acetate : light petroleum = 1 : 15 to 1 : 9) gave the title compound **53** (254 mg, 60%), R_f = 0.25 (ethyl acetate : light petroleum = 1 : 4) (Found: M^+ + H, 389.2227. $C_{25}H_{29}N_2O_2$ requires *M*, 389.2229); ν_{max}/cm^{-1} 3084, 3062, 3028, 2976, 2943, 2867, 2806, 1746, 1494, 1453, 1402, 1357, 1301, 1169, 1106, 1063, 1024, 919, 818 and 744; δ_H (300 MHz, $CDCl_3$) 1.36–1.94 (6 H, m, 3 × CH_2), 2.08 (1 H, d, *J* 12.7 Hz, 5-H), 2.40 (1 H, dd, *J* 1.25, 12.7 Hz, 5-H′), 2.47 (1 H, pent, *J* 8.25 Hz, 6-CH), 3.02 (1 H, d, *J* 14.3 Hz, 3-H), 3.27 and 3.46 (each 1 H, d, *J* 13.0 Hz, Ph*H*CH), 3.71 (1 H, dd, *J* 1.25, 14.3 Hz, 3-H′), 3.81 and 4.31 (each 1 H, d, *J* 15.7 Hz, Ph*H*CH), 4.84 (1 H, s, 1-H), 5.18 and 5.36 (each 1 H, s, 2-CH) and 7.22–7.42 (10 H, m, ArH); δ_C (75 MHz, $CDCl_3$) 17.3, 22.1, 22.2, 38.7, 44.4, 52.1, 55.6, 61.2, 65.5, 78.1, 117.4, 127.2, 127.3, 127.9, 128.3(2), 128.9, 137.8, 138.3, 139.9 and 158.9; *m*/*z* (CI) 389 (M^+ + 1, 30%), 196 (50) and 74 (100).

1-Benzyl-5-benzylamino-5-cyclobutyl-3-formyl-1,2,5,6-tetrahydropyridine (56). Dimethyl sulfoxide (19.6 μL, 0.277 mmol,

3.2 eq.) in DCM (0.5 mL) was added dropwise to oxalyl chloride (14.5 μL, 0.166 mmol, 1.9 eq.) in DCM (0.5 mL) at −78 °C and the reaction mixture stirred at this temperature for 20 min. The alcohol **41** (35 mg, 0.086 mmol) in DCM (0.5 mL) was added and the solution was stirred at −78 °C for 20 min. Hünig's base (96.0 μL, 0.553 mmol, 6.4 eq.) was added and, after stirring for 20 min, the reaction mixture was allowed to warm to rt. After stirring at rt for 3 h, ether (2.5 mL) and saturated aqueous ammonium chloride (5 mL) were added. The aqueous phase was extracted with ether (3 × 5 mL) and the organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography (ethyl acetate : light petroleum = 1 : 4 to 1 : 1) of the residue gave the title compound **56** (29 mg, 93%) as a pale yellow oil, R_f = 0.31 (ethyl acetate : light petroleum = 1 : 1) (Found: M^+ + H, 361.2282. $C_{24}H_{29}N_2O$ requires *M*, 361.2280); ν_{max}/cm^{-1} 3355, 3060, 3028, 2930, 2856, 2808, 2759, 2716, 1685, 1494, 1455, 1363, 1204, 1105, 811 and 742; δ_H (400 MHz, C_6D_6) 1.60–1.95 (6 H, m, 3 × CH_2), 2.01 (1 H, d, *J* 11.2 Hz, 6-H), 2.44 (1 H, m, 5-CH), 2.51 (1 H, d, *J* 11.2 Hz, 6-H′), 3.01 (1 H, dd, *J* 1.5, 16.5 Hz, 2-H), 3.28 and 3.39 (each 1 H, d, *J* 13.0 Hz, PhHC*H*), 3.40 (1 H, d, *J* 16.5 Hz, 2-H′), 3.44 and 3.63 (each 1 H, d, *J* 12.7 Hz, PhHC*H*), 6.33 (1 H, s, 4-H), 7.12–7.42 (10 H, m, ArH) and 9.32 (1 H, s, CHO); δ_C (100 MHz, C_6D_6) 18.0, 22.6, 23.6, 41.6, 47.4, 50.5, 55.6, 57.3, 62.2, 127.0, 127.3, 128.2, 128.4(2), 129.2, 138.5, 141.4, 141.8, 150.8 and 191.3; *m*/*z* (CI^+) 361 (M^+ + 1, 60%) and 108 (100).

(4*SR*,5*RS*)-3-Benzyl-4-(*tert*-butyldimethylsilyloxymethyl)-4-cyclobutyl-5-(1-carboxyethenyl)-1,3-oxazolidin-2-one (58). The Dess–Martin periodinane (984 mg, 2.32 mmol, 2 eq.) was added to the alcohol **32** (500 mg, 1.16 mmol) in DCM (5 mL) at rt and the reaction mixture was stirred at rt for 45 min. Saturated aqueous sodium bicarbonate (5 mL) and saturated sodium bisulfite (3 mL) were added, and the aqueous layer was extracted with ether (3 × 10 mL). The organic extracts were washed with a saturated aqueous sodium bicarbonate (2 × 2 mL) and brine (2 mL), then dried ($MgSO_4$) and concentrated under reduced pressure to provide aldehyde **57**, R_f = 0.44 (ethyl acetate : light petroleum = 3 : 2).

2-Methyl-2-butene (2 M in THF, 5.8 mL, 11.59 mmol, 10 eq.), sodium chlorite (80% technical, 655 mg, 5.79 mmol, 5 eq.) and sodium dihydrogen phosphate (1.39 g, 11.59 mmol, 10 eq.) were added to the aldehyde **57** in *tert*-BuOH and water (1 : 1, 15 mL) and the reaction mixture was stirred at rt for 2 h. Ether (10 mL) and brine (15 mL) were added and the aqueous phase was extracted with ether (3 × 20 mL). The organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure to give the title compound **58** (516 mg, 100%), R_f = 0.35 (ethyl acetate : light petroleum = 1 : 2) (Found: M^+ + H, 446.2351. $C_{24}H_{36}NO_5Si$ requires *M*, 446.2363); ν_{max}/cm^{-1} 2953, 2932, 2885, 2859, 1728, 1631, 1469, 1412, 1359, 1255, 1161, 1102, 840 and 779; δ_H (300 MHz, $CDCl_3$) −0.14 and −0.07 (each 3 H, s, $SiCH_3$), 0.79 [9 H, s, $SiC(CH_3)_3$], 1.41–2.11 (6 H, 3 × CH_2), 2.82 (1 H, pent, *J* 8.5 Hz, 4-CH), 3.41 (2 H, s, 4-CH_2), 4.34 and 4.59 (each 1 H, d, *J* 15.7 Hz, PhHC*H*), 5.40 (1 H, s, 5-H), 6.18 and 6.61 (each 1 H, s, 2′-H), 7.22–7.40 (5 H, m, ArH) and 9.50 (1 H, br. s, OH); δ_C (75 MHz, $CDCl_3$) −6.2, −6.0, 16.9, 18.0, 22.7, 25.7, 38.3, 45.8, 63.4, 69.0, 74.4, 127.3, 128.4, 130.3, 135.4, 138.3, 158.8 and 169.7; *m*/*z* (CI^+) 463 (M^+ + 18, 3%), 446 (M^+ + 1, 5) and 106 (100).

(4*SR*,5*RS*)-3-Benzyl-4-(*tert*-butyldimethylsilyloxymethyl)-4-cyclobutyl-5-[1-(1-hydroxyprop-2-ylaminocarboxy)ethenyl]-1,3-oxazolidin-2-one (59). Isobutyl chloroformate (34 μL, 0.258 mmol, 1.5 eq.) was added to the carboxylic acid **58** (77 mg, 0.172 mmol) and *N*-methylmorpholine (57 μL, 0.515 mmol, 3 eq.) in THF (1.5 mL). After stirring at rt for 1 h, 2-aminopropanol (19 mg, 0.258 mmol, 1.5 eq.) in THF (1.5 mL) was added and the reaction mixture was stirred for 12 h. Saturated aqueous sodium bicarbonate (4 mL) was added and the aqueous layer was extracted with ether (3 × 5 mL). The organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography (ethyl acetate : light petroleum = 3 : 2) gave the title compound **59** (31 mg, 36%), as a mixture of epimers, ratio 1 : 1 (Found: M^+ + H, 503.2941. $C_{27}H_{43}N_2O_5Si$ requires *M*, 503.2941); ν_{max}/cm^{-1} 3355, 2952, 2932, 2858, 1739, 1661, 1616, 1536, 1467, 1411, 1359, 1255, 1095, 842 and 780; *m*/*z* (CI^+) 503 (M^+ + 1, 2%) and 106 (100). Samples were partially separated for NMR; **59a** R_f = 0.25 (ethyl acetate : light petroleum = 3 : 2); δ_H (300 MHz, $CDCl_3$) −0.11 and −0.02 (each 3 H, s, $SiCH_3$), 0.83 [9 H, s, $SiC(CH_3)_3$], 1.22 (3 H, d, *J* 6.7 Hz, 3″-H_3), 1.57–2.10 (6 H, m, 3 × CH_2), 2.95 (1 H, pent, *J* 8.7 Hz, 4-CH), 3.53 (1 H, dd, *J* 5.5, 11.0 Hz, 1″-H), 3.54 and 3.58 (each 1 H, d, *J* 11.0 Hz, 4-HC*H*), 3.63 (1 H, dd, *J* 3.5, 11.0 Hz, 1″-H′), 4.10 (1 H, m, 2″-H), 4.31 and 4.68 (each 1 H, d, *J* = 15.7 Hz, PhHC*H*), 5.48 (1 H, s, 5-H), 5.81 and 5.88 (each 1 H, s, 2′-H), 6.22 (1 H, br. d, *J* 7.5 Hz, NH) and 7.20–7.38 (5 H, m, ArH); δ_C (75 MHz, $CDCl_3$) −6.0, −5.8, 16.9(2), 18.1, 22.5, 22.7, 25.8, 37.4, 45.7, 47.7, 62.6, 66.5, 68.9, 75.5, 121.4, 127.1, 127.2, 128.3, 138.3, 140.3, 158.7 and 167.0; **59b** (still a mixture with **59a**) R_f = 0.19 (ethyl acetate : light petroleum = 3 : 2); δ_H (300 MHz, $CDCl_3$) −0.13 and −0.04 (each 3 H, s, $SiCH_3$), 3.50 and 3.54 (each 1 H, d, *J* 10.5 Hz, 4-HC*H*), 3.71 (1 H, dd, *J* 3.5, 11.0 Hz, 1″-H), 5.53 (1 H, s, 5-H), 5.83 and 5.93 (each 1 H, s, 2′-H) and 6.39 (1 H, br. d, *J* 7.5 Hz, NH). 2-Methylpropyl *N*-(1-hydroxyprop-2-yl) carbamate (33 mg) was also isolated, R_f = 0.35 (ethyl acetate : light petroleum = 3 : 2) (Found: M^+, 175.1210. $C_8H_{17}NO_3$ requires *M*, 175.1208); δ_H (400 MHz, $CDCl_3$) 0.87 (6 H, d, *J* 6.8 Hz, 2 × CH_3), 1.12 (3 H, d, *J* 6.8 Hz, 3′-H_3), 1.86 (1 H, m, 2-H), 3.46 (1 H, dd, *J* 5.1, 11.0 Hz, 1′-H), 3.58 (1 H, dd, *J* 4.0, 11.0 Hz, 1′-H′), 3.72–3.82 (3 H, m, 2′-H, 1-H_2) and 5.8 (1 H, br. s, NH); δ_C (100 MHz, $CDCl_3$) 17.2, 18.9, 27.8, 48.6, 66.4, 71.0 and 157.0; *m*/*z* (CI^+) 176 (M^+ + 1, 100%).

(4*SR*,5*RS*)-3-Benzyl-4-(*tert*-butyldimethylsilyloxymethyl)-4-cyclobutyl-5-[1-(4-methyl-1,3-oxazol-2-yl)ethenyl]-1,3-oxazolidin-2-one (61). The Dess–Martin periodinane (120 mg, 0.283 mmol, 2 eq.) was added to the epimeric alcohols **59** (71 mg, 0.142 mmol) in DCM (2 mL) at rt and the reaction mixture was stirred for 45 min. Saturated aqueous sodium bicarbonate (2 mL) and saturated aqueous sodium bisulfite (1 mL) were added and the aqueous layer was extracted with ether (3 × 5 mL). The organic extracts were washed with saturated aqueous sodium bicarbonate (2 × 1 mL) and brine (1 mL), then dried ($MgSO_4$) and concentrated under reduced

pressure to give the aldehyde **60**, R_f = 0.52 (ethyl acetate : light petroleum = 3 : 2).

2,6-Di-*tert*-butyl-4-methylpyridine (87 mg, 0.425 mmol, 3 eq.) and triphenylphosphine (74 mg, 0.283 mmol, 2 eq.) were added to this aldehyde **60** in DCM (1.5 mL). After cooling to 0 °C, 1,2-dibromotetrachloroethane (92 mg, 0.283 mmol, 2 eq.) was added and the solution was stirred at 0 °C for 1 h. Acetonitrile (1.5 mL) and DBU (42 μL, 0.283 mmol, 2 eq.) were added and the reaction mixture was warmed to rt, stirred for 2.5 h, then concentrated under reduced pressure. Following pre-absorbtion onto silica, chromatography (ethyl acetate : light petroleum = 1 : 50 to 1 : 4) of the residue gave the title compound **61** (29 mg, 42%), R_f = 0.31 (ethyl acetate : light petroleum = 1 : 4) (Found: M^+ + H, 483.2674. $C_{27}H_{39}N_2O_4Si$ requires *M*, 483.2680); ν_{max}/cm^{-1} 3062, 3032, 2954, 2929, 2857, 1755, 1597, 1530, 1469, 1406, 1358, 1256, 1149, 1100, 1031, 1006, 830, 840, 779 and 736; δ_H (300 MHz, $CDCl_3$) −0.25 and −0.18 (each 3 H, s, $SiCH_3$), 0.75 [9 H, s, $SiC(CH_3)_3$], 1.51–1.90 (6 H, m, 3 × CH_2), 2.15 (3 H, d, *J* 1.2 Hz, 4″-CH_3), 2.95 (1 H, pent, *J* 8.7 Hz, 4-CH), 3.42 (2 H, s, 4-CH_2), 4.40 and 4.61 (each 1 H, d, *J* 15.7 Hz, PhHC*H*), 5.70 (1 H, s, 5-H), 5.82 and 6.24 (each 1 H, s, 2′-H) and 7.19–7.38 (6 H, m, ArH); δ_C (75 MHz, $CDCl_3$) −6.3, −6.0, 11.5, 17.0, 18.0, 22.7, 22.8, 25.7, 38.1, 45.5, 62.6, 68.7, 74.9, 120.2, 127.1, 127.2, 128.3, 131.5, 134.2, 137.5, 138.6, 158.7 and 159.6; *m*/*z* (CI^+) 483 (M^+ + 1, 100%).

(4*SR*,5*RS*)-3-Benzyl-4-(*tert*-butyldimethylsilyloxymethyl)-4-cyclobutyl-5-[1-(4-methyl-1,3-oxazol-2-yl)-2-hydroxyethyl]-1,3-oxazolidin-2-one (62). Borane (1 M in THF, 0.6 mL, 0.6 mmol, 7.75 eq.) was added to the alkene **61** (37 mg, 0.078 mmol) in THF (1 mL) at 0 °C and the reaction mixture was stirred at 0 °C for 24 h. Ethanol (0.73 mL), saturated aqueous sodium acetate (2.5 mL) and H_2O_2 (30% in water, 0.83 mL) were added and the reaction mixture was warmed to rt and stirred for 18 h. The aqueous phase was extracted with ether (3 × 5 mL), and the organic extracts were dried ($MgSO_4$) then concentrated under reduced pressure. Chromatography (ethyl acetate : light petroleum = 1 : 10 to 3 : 2) of the residue gave the title compound **62** (8 mg, 20%) as a single diastereoisomer, R_f = 0.34 (ethyl acetate : light petroleum = 1 : 2); ν_{max}/cm^{-1} 3446, 2953, 2932, 2892, 2859, 1750, 1605, 1564, 1467, 1403, 1357, 1295, 1256, 1169, 1102, 979, 938, 843 and 779; δ_H (300 MHz, C_6D_6) −0.07 and −0.03 (each 3 H, s, $SiCH_3$), 0.90 [9 H, s, $SiC(CH_3)_3$], 1.42–1.91 (7 H, m, 3 × CH_2, 1′-H), 1.93 (3 H, s, 4″-CH_3), 2.55 (1 H, pent, *J* 9.0 Hz, 4-CH), 3.55 (1 H, *J* 10.7 Hz, 4-HC*H*), 3.55–3.65 (2 H, m, 2′-H_2), 3.67 (1 H, d, *J* 10.7 Hz, 4-HC*H*), 4.31 and 4.39 (each 1 H, d, *J* 16.0 Hz, PhHC*H*), 4.46 (1 H, d, *J* 5.0 Hz, 5-H), 6.80 (1 H, s, 5″-H) and 7.02–7.20 (5 H, m, ArH); δ_C (75 MHz, C_6D_6) −5.8(2), 11.6, 17.5, 17.6, 18.2, 23.4, 23.9, 25.9, 35.0, 40.1, 45.9, 62.5, 67.2, 80.1, 127.1, 127.2, 128.3, 134.5, 136.5, 139.4, 158.3 and 164.3.

(4*SR*,5*RS*)-3-Benzyl-4-(*tert*-butyldimethylsilyloxymethyl)-4-cyclobutyl-5-propen-2-yl-1,3-oxazolidin-2-one (66). Sodium hydride (60% in mineral oil, 65 mg, 1.60 mmol, 2 eq.) and benzyl bromide (0.475 mL, 4.01 mmol, 5 eq.) were added to the oxazolidinone **25** (261 mg, 0.802 mmol) in THF (4 mL). The reaction mixture was slowly heated to reflux and was stirred under reflux for 1 h before saturated aqueous NH_4Cl (4 mL) was added. The aqueous phase was extracted with ether (3 × 5 mL) and the organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue (light petroleum to 10% ethyl acetate/light petroleum) gave the title compound **66** (3.76 g, 79%), R_f = 0.53 (25% ethyl acetate/light petroleum) (Found: M^+ + H, 416.2619. $C_{24}H_{38}NO_3Si$ requires *M*, 416.2622); ν_{max}/cm^{-1} 3086, 3065, 3032, 2952, 2932, 2859, 1754, 1496, 1468, 1402, 1356, 1292, 1255, 1204, 1162, 1150, 1103, 1004, 906, 840 and 778; δ_H (400 MHz, $CDCl_3$) −0.08 and −0.03 (3 H, s, $SiCH_3$), 0.85 [9 H, s, $SiC(CH_3)_3$], 1.56–2.04 (9 H, m, 3′-H_3, 3 × CH_2), 2.89 (1 H, pent, *J* 8.7 Hz, 4-CH), 3.47 and 3.51 (each 1 H, d, *J* 11.0 Hz, 4-*H*CH), 4.37 and 4.60 (each 1 H, *J* 15.7 Hz, PhHC*H*), 4.88 (1 H, s, 5-H), 5.09 (2 H, s, 1′-H_2) and 7.21–7.38 (5 H, m, ArH); δ_C (100 MHz, $CDCl_3$) −6.1, −5.9, 17.0, 18.1, 19.5, 22.6, 23.0, 25.7, 38.0, 45.7, 62.5, 67.7, 80.2, 115.7, 127.1, 127.4, 128.3, 138.6, 139.9 and 158.8; *m*/*z* (CI) 433 (M^+ + 18, 8%), 416 (M^+ + 1, 10) and 106 (100).

(4*SR*,5*SR*)-5-Acetyl-3-benzyl-4-(*tert*-butyldimethylsilyloxymethyl)-4-cyclobutyl-1,3-oxazolidin-2-one (67). A mixture of ozone and oxygen was bubbled through the alkene **66** (221 mg, 0.532 mmol) in DCM (5 mL) at −78 °C until a persistent blue colour was observed. Triphenylphosphine (167 mg, 0.64 mmmol, 1.2 eq.) was added and the mixture allowed to warm to rt. Chromatography (4% ethyl acetate/light petroleum to 10% ethyl acetate/light petroleum) gave the title compound **67** (206 mg, 93%) as an oil, R_f = 0.43 (25% ethyl acetate/light petroleum) (Found: M^+ + H, 418.2411. $C_{23}H_{36}NO_4Si$ requires *M*, 418.2414); ν_{max}/cm^{-1} 3064, 3031, 2953, 2932, 2859, 1756, 1722, 1469, 1408, 1353, 1255, 1162, 1099, 1070, 1005, 936, 896, 838, 782 and 755; δ_H (300 MHz, $CDCl_3$) 0.03 and 0.07 (each 3 H, s, $SiCH_3$), 0.90 [9 H, s, $SiC(CH_3)_3$], 1.18 (1 H, m, cyclobutyl H), 1.52–1.83 (4 H, m, 2 × CH_2), 2.03 (1 H, pent, *J* 9.8 Hz, 4-CH), 2.33 (1 H, m, cyclobutyl H), 2.41 (3 H, s, 2′-H_3), 3.51 and 3.66 (each 1 H, d, *J* 11.2 Hz, 4-*H*CH), 3.86 (1 H, d, *J* 15.7 Hz, PhHC*H*), 4.63 (1 H, s, 5-H), 4.83 (1 H, d, *J* 15.7 Hz, Ph*H*CH) and 7.25–7.44 (5 H, m, ArH); δ_C (75 MHz, $CDCl_3$) −5.9, −5.7, 17.1, 18.2, 22.3, 22.6, 25.8, 28.8, 38.0, 44.8, 59.6, 71.4, 78.9, 127.6, 128.0, 128.4, 137.7, 157.8 and 207.1; *m*/*z* (CI) 435 (M^+ + 18, 100%) and 418 (M^+ + 1, 20).

(4*SR*,5*SR*)-3-benzyl-4-(*tert*-butyldimethylsilyloxymethyl)-4-cyclobutyl-5-(1-trifluorosulfonyloxyethenyl)-1,3-oxazolidin-2-one (68). Potassium hexamethyldisilazide (0.5 M in toluene, 0.975 mL, 0.486 mmol, 1.3 eq.) was added to the ketone **67** (156 mg, 0.374 mmol) in THF (2 mL) at −78 °C and the solution was stirred at −78 °C for 1 h. *N*-Phenyltrifluoromethanesulfonimide (268 mg, 0.748 mmol, 2 eq.) in THF (1.5 mL) was added and the solution was stirred for 5 h at −78 °C then warmed to rt. Ether (5 mL) and saturated aqueous NH_4Cl (5 mL) were added and the aqueous phase was extracted with ether (3 × 5 mL). The organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue (5% ethyl acetate/light petroleum to 10% ethyl acetate/light petroleum) gave the title compound **68** (145 mg, 71%), R_f = 0.48 (25% ethyl acetate/light petroleum) (Found:

$M^+ + NH_4$, 567.2181, $C_{24}H_{38}N_2O_6F_3SSi$ requires *M*, 567.2172); ν_{max}/cm^{-1} 2954, 2932, 2860, 1765, 1667, 1600, 1497, 1470, 1426, 1256, 1214, 1141, 1108, 1067, 929, 842, 780 and 754; δ_H (400 MHz, $CDCl_3$) −0.04 and 0.01 (each 3 H, s, $SiCH_3$), 0.86 [9 H, s, $SiC(CH_3)_3$], 1.53–1.95 (6 H, m, 3 × CH_2), 2.73 (1 H, pent, *J* 9.0 Hz, 4-CH), 3.60 (2 H, s, 4-CH_2), 4.25 and 4.68 (each 1 H, d, *J* 15.7 Hz, PhHC*H*), 4.91 (1 H, s, 5-H), 5.50 and 5.70 (each 1 H, d, *J* 4.2 Hz, 2′-H) and 7.26–7.39 (5 H, m, ArH); δ_C (100 MHz, $CDCl_3$) −6.1, −6.0, 17.0, 18.0, 22.7, 22.8, 25.6, 38.4, 45.8, 61.8, 68.5, 75.4, 107.5, 118.4 (q, *J* 320 Hz), 127.4, 127.5, 128.5, 137.8, 149.2 and 157.4; δ_F (375 MHz, $CDCl_3$) −69.8; *m*/*z* (CI) 567 (M^+ + 18, 50%), 550 (M^+ + 1, 3) and 225 (100).

(4*SR*,5*SR*)-3-Benzyl-4-(*tert*-butyldimethylsilyloxymethyl)-4-cyclobutyl-5-(1-fur-2-ylethenyl)-1.3-oxazolidin-2-one (65). Lithium chloride (11 mg, 0.27 mmol), CuI (9 mg, 0.045 mmol), $Pd(PPh_3)_4$ (3 mg, 2.5% mol) and 2-tributylstannylfuran (85 μL, 0.27 mmol) were added to the vinyl triflate **68** (50 mg, 0.09 mmol) in THF (2 mL) and the reaction mixture heated under reflux for 3 h. After concentration under reduced pressure, chromatography of the residue (light petroleum to 2% ethyl acetate/light pretroleum) gave the title compound **65** (27 mg, 65% yield) as a colourless oil, R_f 0.35 (50% ether/light petroleum) (Found: M^+ + Na, 490.2379. $C_{27}H_{37}O_4NNaSi$ requires *M*, 490.2384); ν_{max}/cm^{-1} 2928, 2853, 2361, 1754, 1254, 1107 and 837; δ_H (500 MHz, $CDCl_3$) 0.00 and 0.05 (each 3 H, s, $SiCH_3$), 0.99 [9 H, s, $SiC(CH_3)_3$], 1.77–2.24 (6 H, m, 3 × CH_2), 3.11 (1 H, pent, *J* 9.0 Hz, 4-CH), 3.54 and 3.69 (each 1 H, d, *J* 11.0 Hz, 4-HC*H*), 4.60 and 4.85 (each 1 H, d, *J* 15.8 Hz, Ph*H*CH), 5.59 and 5.70 (each 1 H, d, *J* 1.0 Hz, 2′-H) 5.99 (1 H, s, 5-H), 6.61 (1 H, dd, *J* 3.5 Hz, 2.0 Hz, 4″-H), 6.63 (1 H, d, *J* 3.5 Hz, 3″-H), 7.41–7.54 (5 H, m, ArH) and 7.59 (1 H, d, *J* 1.5 Hz, 5″-H); δ_C (125 MHz, $CDCl_3$) −6.2, −6.0, 17.0, 18.0, 22.7, 22.9, 25.8, 37.8, 45.8, 62.7, 68.5, 76.0, 106.9, 111.5, 114.6, 127.0, 127.2, 128.3, 132.9, 138.6, 142.1, 152.1 and 158.8; *m*/*z* (ES^+) 490 (M^+ + 23, 100%).

n-Butyllithium (1.6 M in hexanes, 180 μL, 0.28 mmol) was added to methyltriphenylphosphonium bromide (103 mg, 0.28 mmol) in THF (1 mL) and the reaction mixture was stirred at room temperature for 1 h. The ketone **74** (90 mg, 0.19 mmol) in THF (0.9 mL) was added dropwise and the reaction mixture was stirred at room temperature for 15 minutes. Saturated aqueous NH_4Cl was added and the aqueous phase was extracted with ethyl acetate. The organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue (10% ethyl acetate/light pretroleum) gave the title compound **65** (75 mg, 85% yield).

n-Butyllithium (1.6 M in hexanes, 10.1 mL, 16.2 mmol) was added to the vinyl stannane **76** (6.2 g, 16.2 mmol) in tetrahydrofuran (125 mL) dropwise at −78 °C and the reaction mixture was stirred at this temperature for 10 min. The aldehyde **10** (2.9 g, 7.4 mmol) in tetrahydrofuran was added dropwise, stirring was continued at −78 °C for 20 min, the reaction mixture was allowed to warm to room temperature, and stirring was continued for 16 h. Saturated aqueous NH_4Cl (50 mL) was added and the aqueous layer was extracted with ether (3 × 50 mL). The organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure to yield the oxazolidinone **77** as a yellow oil. Sodium hydride (60% dispersion in paraffin, 422 mg, 10.5 mmol) and benzyl bromide (1.4 mL, 15 mmol) were added to the oxazolidinone **77** in tetrahydrofuran (25 mL) at 0 °C and the reaction mixture heated under reflux for 6 h. Saturated aqueous NH_4Cl (50 mL) was added and the aqueous phase extracted with ether (3 × 50 mL). The organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography of the residue (20% ether/light petroleum) gave the title compound **65** (2.7 g, 78% from **10**) as a viscous oil, R_f 0.24 (20% ether/light petroleum).

(4*SR*,5*SR*)-3-Benzyl-4-(*tert*-butyldimethylsilyloxymethyl)-4-cyclobutyl-5-[1-(2-phenyloxazol-5-yl)ethenyl]-1,3-oxazolidin-2-one (69). *n*-Butyllithium (2.5 M in THF, 0.45 mL, 1.12 mmol, 6 eq.) was added to 5-bromo-2-phenyl-1,3-oxazole (235 mg, 1.05 mmol, 6 eq.) in THF (2 mL) at −18 °C and the resulting suspension was stirred for 45 min. Zinc chloride (0.5 M in THF, 2.6 mL, 1.30 mmol, 7.5 eq.) was added and the solution was warmed to rt, stirred for 30 min and then added to the enol triflate **68** (95 mg, 0.173 mmol) and $PdCl_2(PPh_3)_2$ (12 mg, 0.017 mmol, 10 mol%) in THF (1 mL). After being stirred for 48 h at rt, saturated aqueous NH_4Cl (5 mL) was added and the aqueous layer was extracted with ether (3 × 10 mL). The organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue (2% to 3% ethyl acetate/light petroleum) gave the title compound **69** (34 mg, 80%, 45% conversion), R_f = 0.35 (25% ethyl acetate/light petroleum) (Found: M^+ + H, 545.2844. $C_{32}H_{41}N_2O_4Si$ requires *M*, 545.2835); ν_{max}/cm^{-1} 3064, 3032, 2952, 2930, 2858, 1756, 1693, 1646, 1470, 1404, 1360, 1255, 1101, 1020, 840 and 778; δ_H (300 MHz, $CDCl_3$) −0.13 and −0.09 (each 3 H, s, $SiCH_3$), 0.81 [9 H, s, $SiC(CH_3)_3$], 1.58–2.11 (6 H, m, 3 × CH_2), 2.90 (1 H, pent, *J* 8.7 Hz, 4-CH), 3.49 and 3.56 (each 1 H, d, *J* 11.0 Hz, 4-*H*CH), 4.41 and 4.71 (each 1 H, d, *J* 16.0 Hz, Ph*H*CH), 5.31 (1 H, s, 5-H), 5.69 and 5.89 (each 1 H, s, 2′-H), 7.25–7.57 (9 H, m, ArH) and 8.05–8.12 (2 H, m, ArH); δ_C (75 MHz, $CDCl_3$) −6.2, −6.0, 16.9, 18.0, 22.8, 23.1, 25.7, 38.2, 46.0, 62.4, 68.7, 76.4, 116.7, 125.0, 126.4, 126.9, 127.3, 127.4, 128.4, 128.9, 130.7, 133.3, 138.4, 149.3, 158.7 and 161.3; *m*/*z* (CI) 545 (M^+ + 1, 2%), 289 (50) and 181 (100).

(4*SR*,5*RS*)-4-(*tert*-Butyldimethylsilyloxymethyl)-4-cyclobutyl-5-ethenyl-1,3-oxazolidin-2-one (70). Ethenylmagnesium bromide in tetrahydrofuran (0.7 M in THF, 26.3 mL, 20.24 mmol) was added to the aldehyde **10** (3.6 g, 9.2 mmol) in tetrahydrofuran (92 mL) at −78 °C and the solution was stirred for 2 h at −78 °C then for 16 h at rt. Saturated aqueous NH_4Cl (50 mL) was added and the solution concentrated under reduced pressure. The aqueous residue was extracted with ether (3 × 50 mL) and organic extracts were dried ($MgSO_4$) then concentrated under reduced pressure. Chromatography of the residue (25% ether/light petroleum) gave the title compound **70** (2.6 g, 91%) as a clear oil, R_f 0.6 (25% ether/light petroleum) (Found: M^+ + Na, 334.1812. $C_{16}H_{29}O_3NNaSi$ requires *M*, 334.1809); ν_{max}/cm^{-1} 3210, 3132, 2951, 2930, 2858, 1749, 1472, 1464, 1429, 1370, 1290, 1256, 1108, 1070, 1023, 990, 940 and 838; δ_H (500 MHz, $CDCl_3$) 0.00 and 0.01 (each 3 H, s,

$SiCH_3$), 0.84 [9 H, s, $SiC(CH_3)_3$], 1.67–2.10 (6 H, m, 3 × CH_2), 2.50 (1 H, m, 4-CH), 3.36 and 3.39 (each 1 H, d, *J* 10.5 Hz, 4-*H*CH), 4.51 (1 H, d, *J* 7.0 Hz, 5-H), 5.27 (1 H, d, *J* 10.5 Hz, 2′-H), 5.34 (1 H, d, *J* 17.0 Hz, 2′-H′), 5.95 (1 H, ddd, *J*, 17.0, 10.5, 6.0 Hz, 1′-H) and 6.42 (1 H, s, NH); *m*/*z* (ES^-) 310 ($M^+ - 1$, 100%).

(4*SR*,5*RS*)-3-Benzyl-4-(*tert*-butyldimethylsilyloxymethyl)-4-cyclobutyl-5-ethenyl-1,3-oxazolidin-2-one (71). Sodium hydride (60% dispersion in paraffin, 120 mg, 3 mmol) and benzyl bromide (0.47 mL, 4 mmol) were added at 0 °C to the oxazolidinone **70** (615 mg, 1.97 mmol) in tetrahydrofuran (15 mL) and the reaction mixture was heated under reflux for 6 h. Saturated aqueous NH_4Cl (50 mL) was added and the solution concentrated under reduced pressure. The residue was extracted with ether (3 × 50 mL) and the organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography of the residue (light petroleum to 40% ether/light petroleum) gave the title compound **71** (670 mg, 86%) as a viscous oil, R_f 0.25 (15% ether/light petroleum) (Found: M^+ + Na, 424.2281. $C_{23}H_{35}O_3NNaSi$ requires *M*, 424.2278); ν_{max}/cm^{-1} 2929, 1752, 1402, 1252, 1108, 838 and 777; δ_H (500 MHz, $CDCl_3$) 0.00 (6 H, s, 2 × $SiCH_3$), 0.87 [9 H, s, $SiC(CH_3)_3$], 1.29–1.87 (6 H, m, 3 × CH_2), 2.52 (1 H, m, 4-CH), 3.49 (2 H, s, 4-CH_2), 4.03 and 4.65 (each 1 H, d, *J* 15.8 Hz, Ph*H*CH), 4.82 (1 H, d, *J* 7.6 Hz, 5-H), 5.36 (1 H, d, *J*, 10.5 Hz, 2′-H), 5.48 (1 H, d, *J* 16.0 Hz, 2′-H′), 6.04 (1 H, ddd, *J* 18.0, 9.8, 7.6 Hz, 1′-H) and 7.2–7.35 (5 H, m, ArH); δ_C (125 MHz, $CDCl_3$) −5.8, 17.5, 18.0, 22.6, 25.7, 38.2, 45.3, 61.7, 67.8, 79.8, 120.8, 127.3, 127.8, 128.4, 132.6, 138.5 and 158.9; *m*/*z* (ES^+) 424 (M^+ + 23, 100%).

(4*RS*,5*RS*)-3-Benzyl-4-(*tert*-butyldimethylsilyloxymethyl)-4-cyclobutyl-5-formyl-1,3-oxazolidin-2-one (72). A mixture of O_2 and O_3 were bubbled through a solution of the alkene **71** (1.87 g, 4.65 mmol) in dichloromethane (50 mL) at −78 °C until the solution assumed a pale blue colour. Triphenylphosphine (1.36 g, 5.56 mmol) was added immediately and reaction mixture was stirred at rt for 3 h. After concentration under reduced pressure, chromatography of the residue (25% ether/light petroleum to neat ether) gave the title compound **72** (1.7 g, 90%), R_f 0.1 (20% ether/light petroleum) (Found: M^+ + H, 404.2258. $C_{23}H_{34}O_4NSi$ requires *M*, 404.2252); ν_{max}/cm^{-1} 2929, 2854, 2357, 1755, 1738, 1406, 1101 and 838; δ_H (500 MHz, $CDCl_3$) 0.00 and 0.01 (each 3 H, s, $SiCH_3$), 0.89 [9 H, s, $SiC(CH_3)_3$], 1.20–2.06 (6 H, m, 3 × CH_2), 2.39 (1 H, m, 4-CH), 3.42 and 3.49 (each 1 H, d, *J* 11.0 Hz, 4-*H*CH), 3.94 (1 H, d, *J* 15.5 Hz, Ph*H*CH), 4.65 (1 H, d, *J* 1.0 Hz, 5-H), 4.71 (1 H, d, *J* 15.5 Hz, PhHC*H*), 7.26–7.38 (5 H, m, ArH) and 9.82 (1 H, d, *J* 1.0 Hz, CHO); δ_C (125 MHz, $CDCl_3$) −5.8, 17.3, 17.9, 22.4, 25.6, 37.0, 44.9, 59.3, 72.6, 78.6, 127.8, 128.2, 128.6, 137.5, 157.9 and 199.9; *m*/*z* (ES^-) 402 ($M^+ - 1$, 100%).

(4*SR*,5*SR*)-3-Benzyl-4-(*tert*-butyldimethylsilyloxymethyl)-4-cyclobutyl-5-(fur-2-ylhydroxymethyl)-1,3-oxazolidin-2-one (73). *n*-Butyllithium (1.6 M in hexanes, 0.73 mL, 1.2 mmol) was added to furan (85 μL, 1.2 mmol) in tetrahydrofuran (2.4 mL) at −78 °C. The reaction mixture was warmed to rt and stirred for 1.5 h, then cooled to −78 °C and the aldehyde **72** (157 mg, 0.39 mmol) in tetrahydrofuran (1.2 mL) was added. The mixture was stirred at −78 °C for 5 h, and then saturated aqueous NH_4Cl (5 mL) was added. The mixture was concentrated under reduced pressure and the residue extracted with ether (3 × 5 mL). The organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography of the residue (20% ether/light petroleum) gave the alcohol **73** (110 mg, 60%) as a mixture of diastereoisomers. Data for the less polar title compound **73a**, R_f 0.52 (50% ether/light petroleum) (Found: M^+ + H, 472.2505. $C_{26}H_{38}O_5NSi$ requires *M*, 472.2514); ν_{max}/cm^{-1} 3385, 2956, 2858, 2351, 2336, 1728, 1411, 1256, 1106 and 838; δ_H (500 MHz, $CDCl_3$) −0.01 and 0.00 (each 3 H, s, $SiCH_3$), 0.83 [9 H, s, $SiC(CH_3)_3$], 1.54–2.16 (6 H, m, 3 × CH_2), 2.70 (1 H, m, 4-CH), 3.46 (1 H, d, *J* 4.5 Hz, OH), 3.58 and 3.66 (each 1 H, d, *J* 11.4 Hz, 4-*H*CH), 4.33 and 4.42 (each 1 H, d, *J* 16.0 Hz, Ph*H*CH), 4.67 (1 H, d, *J* 8.8 Hz, 5-H), 5.07 (1 H, dd, *J* 8.8, 4.5 Hz, 5-CH), 6.34 (1 H, dd, *J* 3.2, 1.5 Hz, 4′-H), 6.38 (1 H, d, *J* 3.2 Hz, 3′-H), 7.21–7.32 (5 H, m, ArH) and 7.4 (1 H, d, *J* 1.5 Hz, 5′-H); δ_C (125 MHz, $CDCl_3$) −6.0(2), 17.5, 18.0, 23.2, 23.3, 25.7, 39.4, 45.4, 62.3, 66.0, 68.1, 78.0, 108.7, 110.5, 127.6, 127.8, 128.6, 138.5, 142.5, 152.8 and 158.2; *m*/*z* (ES^-) 470.3 ($M^+ - 1$, 100%). Data for the more polar title compound **73b** R_f 0.37 (50% ether/light petroleum) (Found: M^+ + Na, 494.2327. $C_{26}H_{37}O_5NNaSi$ requires *M*, 494.2333); ν_{max}/cm^{-1} 3375, 2956, 2853, 2367, 2326, 1742, 1403, 1259, 1096 and 838; δ_H (500 MHz, $CDCl_3$) 0.00 and 0.01 (each 3 H, s, $SiCH_3$), 0.85 [9 H, s, $SiC(CH_3)_3$], 1.38–1.82 (6 H, m, 3 × CH_2), 2.29 (1 H, m, 4-CH), 3.22 (1 H, d, *J* 4.5 Hz, OH), 3.64 and 3.66 (each 1 H, d, *J* 11.4 Hz, 4-*H*CH), 4.13 and 4.57 (each 1 H, d, *J* 16.0 Hz, Ph*H*CH), 4.69 (1 H, d, *J* 4.5 Hz, 5-H), 5.12 (1 H, t, *J* 4.5 Hz, 5-CH), 6.34 (1 H, dd, *J* 3.2, 1.6 Hz, 4′-H), 6.40 (1 H, d, *J* 3.2 Hz, 3′-H), 7.18–7.30 (5 H, m, ArH) and 7.36 (1 H, d, *J* 1.0 Hz, 5′-H); δ_C (125 MHz, $CDCl_3$) −5.9, −5.8, 17.3, 18.0, 22.8, 23.0, 25.7, 39.2, 45.3, 61.7, 66.2, 67.4, 78.7, 108.3, 110.7, 127.4, 127.5, 128.5, 138.1, 142.3, 152.7 and 158.4; *m*/*z* (ES^-) 470.4 ($M^+ - 1$, 100%).

(4*RS*,5*RS*)-3-Benzyl-4-(*tert*-butyldimethylsilyloxymethyl)-4-cyclobutyl-5-furoyl-1,3-oxazolidin-2-one (74). Tetrapropyl perruthenate (102 mg, 0.29 mmol) was added to a mixture of the epimeric alcohols **73** (1.37 g, 2.9 mmol), *N*-methylmorpholine *N*-oxide (512 mg, 4.4 mmol) and 4 Å molecular sieves (1.4 g) in dichloromethane (29 mL) and the reaction mixture was stirred for 2 h at rt. After filtering through Celite, the filtrate was concentrated under reduced pressure and chromatography of the residue (light petroleum to 20% ether/light petroleum) gave title compound **74** (1.21 g, 85%) as a colourless oil, R_f 0.47 (50% ether/light petroleum) (Found: M^+ + Na, 492.2175. $C_{26}H_{35}O_5NNaSi$ requires *M*, 492.2177); ν_{max}/cm^{-1} 2929, 2853, 1755, 1664, 1464, 1409, 1254, 1104, 838 and 777; δ_H (500 MHz, $CDCl_3$) 0.00 and 0.09 (each 3 H, s, $SiCH_3$), 0.90 [9 H, s, $SiC(CH_3)_3$], 1.51–2.44 (6 H, m, 3 × CH_2), 2.72 (1 H, m, 4-CH), 3.77 and 3.97 (each 1 H, d, *J* 11.4 Hz, 4-*H*CH), 4.42 and 5.02 (each 1 H, d, *J* 15.8 Hz, Ph*H*CH), 5.35 (1 H, s, 5-H), 6.80 (1 H, dd, *J* 3.5, 2.0 Hz, 4′-H), 7.50–7.63 (5 H, m, ArH), 7.89 (1 H, d, *J* 2.0 Hz, 5′-H) and 7.95 (1 H, d, *J* 3.5 Hz, 3′-H); δ_C (125 MHz, $CDCl_3$) −6.2, −6.0, 17.2, 18.0, 22.7, 22.9, 25.5, 38.6, 45.1, 59.9, 71.7, 78.0, 112.6, 122.3, 127.6, 128.0, 128.5, 137.8, 147.0, 150.6, 157.8 and 184.1; *m*/*z* (ES^+) 492 (M^+ + 23, 100%).

1-(Fur-2-yl)ethenyl(tributyl)stannane (76). *n*-Butyllithium in hexanes (1.6 M in hexanes, 31.2 mL, 50 mmol) was added dropwise to di-isopropylamine (7.1 mL, 50 mmol) in tetrahydrofuran (244 mL) at 0 °C and the solution was stirred for 30 min. Tributyltin hydride (12.2 mL) was added dropwise and the solution was stirred for a further 30 min. Furyl methyl ketone **75** (5.0 g, 45.4 mmol) in tetrahydrofuran (9.1 mL) was added and the solution was warmed to rt and stirred until judged complete by TLC (*ca.* 1 h). Mesyl chloride (14.8 mL, 182 mmol) and triethylamine (47 mL, 340 mmol) were added and the reaction mixture stirred at rt overnight. The mixture was dissolved in MeCN (500 mL) and extracted with pentane (3 × 500 mL). The pentane extracts were concentrated under reduced pressure and chromatography of the residue (pentane) gave the title compound **76** (8.4 g, 59%) a mobile yellow oil that was used without delay, R_f 0.95 (pentane); δ_H (300 MHz, $CDCl_3$) 0.90 (9 H, t, *J* 7.0 Hz, 3 × CH_3), 1.05 (6 H, m, 3 × CH_2), 1.35 (6 H, pent, *J* 7.0 Hz, 3 × CH_2), 1.45–1.62 (6 H, m, 3 × CH_2), 5.22 (1 H, d, *J* 2.5 Hz, 2-H), 6.15 (1 H, d, *J* 3.5 Hz, 3′-H), 6.19 (1 H, d, *J* 2.5 Hz, 2-H′), 6.28 (1 H, dd, *J* 3.5, 1.8 Hz, 4′-H) and 7.27 (1 H, d, *J* 1.8 Hz, 5′-H); δ_C (125 MHz, $CDCl_3$) 10.1, 13.7, 27.5, 28.9, 106.0, 111.2, 122.6, 139.8, 141.4 and 158.6.

(4*RS*,5*SR*)-3-Benzyl-4-(*tert*-butyldimethylsilyloxymethyl)-4-cyclobutyl-5-(1-fur-2-yl-2-hydroxyethyl)-1,3-oxazolidin-2-ones (78) and (79). Borane in THF (1 M, 3.85 mL, 3.85 mmol) was added to the alkene **65** (600 mg, 1.28 mmol) in CH_2Cl_2 (3.5 mL) at 0 °C. The mixture allowed to warm at room temperature, stirred 3 h, then was cooled to 0 °C and $NaBO_3{\cdot}4H_2O$ (590 mg, 3.84 mmol) and water were added carefully. The mixture was stirred at rt overnight and then the aqueous phase was extracted with ethyl acetate and the organic extracts were dried ($MgSO_4$). After concentration under reduced pressure, chromatography of the residue (light petroleum to 20% ethyl acetate/light petroleum) gave a mixture of the title compounds **78** and **79** (390 mg, 60%), **78 : 79** = 2 : 1 (^{1}H NMR), R_f 0.20 (20% ethyl acetate/light petroleum); ν_{max}/cm^{-1} 3420, 2953, 2930, 2858, 1738, 1732, 1411, 1361, 1257, 1104, 1072, 836, 778 and 733; δ_H (500 MHz, $CDCl_3$) major isomer **78** −0.17 and −0.19 (each 3 H, s, $SiCH_3$), 0.81 [9 H, s, $OSi(CH_3)_3$], 1.46–2.00 (6 H, m, 3 × CH_2), 2.08 (1 H, br. s, OH), 3.03 (1 H, pent, *J* 8.8 Hz, 4-CH), 3.39 (1 H, d, *J* 10.4 Hz, 4-*H*CH), 3.43 (1 H, m, 1′-H), 3.46 (1 H, d, *J* 10.4 Hz, 4-HC*H*), 3.83 (1 H, dd, *J* 6.3, 10.7 Hz, 2′-H), 3.98 (1 H, m, 2′-H′), 4.16 and 4.53 (each 1 H, d, *J* 15.8 Hz, PhHC*H*), 5.06 (1 H, d, *J* 1.3 Hz, 5-H), 6.40 (2 H, narrow m, 3″-H and 4″-H), 6.87–6.89 (2 H, m, ArH), 7.15–7.18 (3 H, m, ArH) and 7.34 (1 H, m, ArH); minor isomer **79** −0.09 and −0.14 (3 H, s, $SiCH_3$), 0.93 [9 H, s, $Si(CH_3)_3$], 3.54 (1 H, d, *J* 11.3 Hz, 4-*H*CH), 3.68 (1 H, m, 1′-H), 3.72 (1 H, d, *J* 11.3 Hz, 4-HC*H*), 3.94–4.00 (2 H, m, 2′-H, Ph*H*CH), 4.04 (1 H, dd, *J* 4.7, 11.0 Hz, 2′-H′), 4.64 (1 H, d, *J* 10.7 Hz, 5-H), 4.84 (1 H, d, *J* 16.1 Hz, PhHC*H*), 6.26 (1 H, d, *J* 3.1 Hz, 3″-H) and 6.37 (1 H, dd, *J* 2.2, 3.1 Hz, 4″-H); δ_C (75 MHz, $CDCl_3$) major isomer **78** −6.1, 17.4, 18.1, 22.6, 23.5, 25.8, 39.4, 41.9, 45.2, 63.6, 63.9, 66.2, 75.0, 108.8, 111.2, 126.9, 127.4, 128.3, 138.0, 141.3, 150.9 and 158.4; minor isomer **79** −5.8, −5.6, 16.8, 17.8, 22.8, 25.6, 37.7, 41.4, 45.8, 59.7, 64.1, 69.7, 77.6, 108.3, 110.9, 127.0, 127.1, 128.5, 138.3, 142.0, 152.2 and 159.3.

(4*RS*,5*SR*)-3-Benzyl-4-hydroxymethyl-4-cyclobutyl-5-(1-fur-2-yl-2-hydroxyethyl)-1,3-oxazolidin-2-ones (80) and (81). Tetrabutylammonium fluoride (1 M in THF, 155 μL, 0.155 mmol) was added to a mixture of the silyl ethers **78** and **79** (63 mg, 0.13 mmol) in THF (0.5 mL) at 0 °C and the mixture stirred at rt for 30 min. Brine was added and the mixture was extracted with ethyl acetate. The organic extracts were dried ($MgSO_4$) and concentrated under reduced presure. Chromatography of the residue (60% ethyl acetate/light petroleum) gave the the title compound **80** (30 mg, 62%) as an oil, R_f 0.28 (60% ethyl acetate/light petroleum); δ_H (500 Mz, $CDCl_3$) 1.50 (2 H, br. s, 2 × OH), 1.50–2.00 (6 H, m, 3 × CH_2), 2.92 (1 H, pent. *J* 7.0 Hz, 4-CH), 3.34 (1 H, m, 1′-H), 3.55 and 3.44 (each 1 H, d, *J* 14.1 Hz, 4-*H*CH), 3.79 (1 H, dd, *J* 9.0, 4.7 Hz, 2′-H), 3.92 (1 H, t, *J* 9.0 Hz, 2′-H′), 4.12 and 4.44 (each 1 H, d, *J* 16.8 Hz, Ph*H*CH), 4.97 (1 H, s, 5-H), 6.35 and 6.38 (each 1 H, narrow m, 3″-H and 4″-H), 6.94 (2 H, m, ArH), 6.94–7.23 (3 H, m, ArH) and 7.30 (1 H, s, ArH); *m*/*z* (ES^+) 394 (M^+ + 23, 100%). The second fraction was the title compound **81** (12 mg, 28%) as an oil, R_f 0.13 (60% ethyl acetate/light petroleum); δ_H (500 Mz, $CDCl_3$) 1.30–1.80 (6 H, m, 3 × CH_2), 2.08 (1 H, pent. *J* 7.0 Hz, 4-CH), 3.29 and 3.44 (each 1 H, d, *J* 14.1 Hz, 4-*H*CH), 3.78 (1 H, m, 1′-H), 3.92 and 3.98 (each 1 H, dd, *J* 9.0, 13.0 Hz, 2′-H), 4.34 and 4.47 (each 1 H, d, *J* 17.1 Hz, Ph*H*CH), 4.69 (1 H, d, *J* 10.7 Hz, 5-H), 6.21 and 6.27 (each 1 H, narrow m, 3″-H and 4″-H) and 7.20–7.39 (6 H, m, ArH); *m*/*z* (ES^+) 394 (M^+ + 23, 100%).

(4*RS*,5*SR*)-3-Benzyl-4-cyclobutyl-5-(1-fur-2-ylethenyl)-4-hydroxymethyloxazolidin-2-one (82). Tetrabutylammonium fluoride (1 M in THF, 0.24 mL, 0.24 mmol) was added to the silyl ether **65** (108 mg, 0.23 mmol) in tetrahydrofuran (2.3 mL) at rt and the solution stirred for 1 h. Saturated aqueous NH_4Cl (5 mL) was added and the mixture concentrated under reduced pressure. The residue was extracted with ether (4 × 5 mL) and the organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography of the residue (50% ether/light petroleum) gave the title compound **82** (82 mg, *ca.* 100%) as a viscous oil, R_f 0.12 (50% ether/light petroleum) (Found: M^+ + Na, 376.1529. $C_{21}H_{23}O_4NNa$ requires *M*, 376.1519); ν_{max}/cm^{-1} 3427, 2944, 2361, 1750, 1495, 1435, 1409, 1358, 1289, 1149, 1063, 1017, 918, 885 and 744; δ_H (500 MHz, $CDCl_3$) 1.26 (1 H, br. s, OH), 1.53–1.98 (6 H, m, 3 × CH_2), 2.75 (1 H, pent, *J* 9 Hz, 4-CH), 3.29 and 3.34 (each 1 H, dd, *J* 12.5, 4.0 Hz, 4-HC*H*), 4.45 and 4.49 (each 1 H, d, *J* 16.5 Hz, Ph*H*CH), 5.32 (1 H, s, 5-H), 5.39 and 5.73 (each 1 H, s, 2′-H), 6.34 (1 H, dd, *J* 3.5, 2.0 Hz, 4″-H), 6.41 (1 H, d, *J* 3.5 Hz, 3″-H), 7.17–7.32 (5 H, m, ArH) and 7.33 (1 H, d, *J* 1.5 Hz, 5″-H); δ_C (125 MHz, $CDCl_3$) 17.2, 22.8, 22.9, 38.2, 45.7, 61.8, 68.7, 76.1, 107.4, 111.6, 114.2, 127.6, 128.7, 133.6, 138.4, 142.5, 151.6 and 158.8; *m*/*z* (ES^+) 371 (M^+ + 18, 100%).

(4*RS*,5*SR*)-3-Benzyl-4-cyclobutyl-5-(1-fur-2-ylethenyl)-4-(prop-2-enylamino)methyl-1,3-oxazolidin-2-one (84). The Dess–Martin periodinane (70 mg, 0.17 mmol) was added to the alcohol **82** (39 mg, 0.11 mmol) in dichloromethane (1.1 mL) at

rt and the solution was stirred for 2 h. Concentration under reduced pressure gave the aldehyde **83** (31 mg, 80%), R_f 0.46 (50% ether/light petroleum) (Found: M^+ + Na, 374.1369. $C_{21}H_{21}O_4NNa$ requires *M*, 374.1363); ν_{max}/cm^{-1} 2924, 2846, 1760, 1732, 1393, 1287, 1059, 1018, 920 and 807; δ_H (500 MHz, $CDCl_3$) 1.40–2.05 (6 H, m, 3 × CH_2), 2.90 (1 H, m, 4-CH), 4.31 amd 4.45 (each 1 H, d, *J* 15.0 Hz, PhC*H*CH), 5.35 and 5.40 (each 1 H, s, 2′-H), 5.72 (1 H, s, 5-H), 6.30 and 6.34 (each 1 H, s, 3″-H and 4″-H), 7.15–7.30 (6 H, m, ArH) and 8.90 (1 H, s, CHO); δ_C (125 MHz, $CDCl_3$) 18.1, 22.7, 23.4, 37.1, 46.3, 73.1, 75.9, 108.6, 111.7, 114.8, 128.1, 128.3, 128.7, 131.8, 137.0, 142.8, 150.0, 158.1 and 197.3; *m*/*z* (ES^+) 374 (M^+ + 23, 100%) and 352 (M^+ + 1, 40).

This aldehyde **83** was taken up in dry dichloromethane (0.3 mL), prop-2-enylamine (12 μL, 1.52 mmol) and oven dried $MgSO_4$ (44 mg, 0.36 mmol) were added, and the mixture was stirred under reflux for 16 h. After filtration through Celite and concentration of the filtrate under reduced pressure, the residue was immediately dissolved in methanol (0.6 mL) and acetic acid (6.2 μL, 0.106 mmol) and $NaCNBH_3$ (1 M in THF, 122 μL, 0.122 mmol) were added. The reaction mixture was stirred at rt for 1 h and then saturated aqueous $NaHCO_3$ (5 mL) was added. The aqueous mixture was extracted with ether (5 × 5 mL) and the organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue (20% ether/light petroleum) gave the title compound **84** (25 mg, 56%) as a white foam that slowly crystallised from ether, R_f 0.51 (50% ether/light petroleum) (Found: M^+ + H, 393.2170. $C_{24}H_{29}O_3N_2$ requires *M*, 393.2173); ν_{max}/cm^{-1} 3343, 2945, 2359, 2341, 1744, 1644, 1495, 1456, 1404, 1360, 1287, 1149, 1061, 1017, 919, 806 and 744; δ_H (500 MHz, $CDCl_3$) 1.47–1.95 (6 H, m, 3 × CH_2), 2.23 and 2.37 (each 1 H, d, *J* 13.5 Hz, 4-*H*CH), 2.72 (3 H, m, 4-CH and 1′-H_2), 4.41 and 4.54 (each 1 H, d, *J* 15.8 Hz, PhC*H*CH), 4.86 (1 H, dd, *J* 16.5, 1.6 Hz, 3′-H), 4.87 (1 H, dd, *J* 10.0, 1.6 Hz, 3′-H′), 5.28 (1 H, s, 2″-H), 5.38 (1 H, s, 2″-H′), 5.52 (1 H, ddt, *J* 16.5, 10.0, 6.0 Hz, 2′-H), 5.70 (1 H, s, 5-H), 6.33 (1 H, dd, *J* 3.5, 1.5 Hz, 4‴-H), 6.37 (1 H, d, *J* 3.5 Hz, 3‴-H) and 7.14–7.32 (6 H, m, ArH); δ_C (125 MHz, $CDCl_3$) 17.1, 23.2, 23.4, 39.9, 46.0, 50.0, 53.0, 68.5, 76.9, 107.3, 111.8, 114.3, 115.9, 127.5, 127.8, 128.7, 134.1, 136.7, 138.9, 142.4, 152.3 and 159.1; *m*/*z* (ES^+) 393 (M^+ + 1, 100%).

(4*RS*,5*SR*)-4-Aminomethyl-3-benzyl-4-cyclobutyl-5-(1-fur-2-ylethenyl)-1,3-oxazolidin-2-one (85). Tetrakis-triphenylphosphine palladium (2.5 mg, 1 mol%) was added to the propenylamine **84** (82 mg, 0.23 mmol) and 1,3-dimethylbarbituric acid (99 mg, 0.69 mmol) in dichloromethane (0.5 mL) at rt and the reaction mixture was stirred at 35 °C for 2 h. Saturated aqueous $NaHCO_3$ (5 mL) and ether (5 mL) were added and the aqueous layer was extracted with ether (3 × 5 mL). The organic extracts were dried (Na_2SO_4) then concentrated under reduced pressure. Chromatography of the residue (70% ether/light petroleum) gave the title compound **85** (48 mg, 74%) as a white foam, R_f 0.31 (ether) (Found: M^+ + H, 353.1857. $C_{21}H_{25}O_3N_2$ requires *M*, 353.1860); ν_{max}/cm^{-1} 3407, 2943, 2868, 2360, 2342, 1739, 1622, 1496, 1404, 1359, 1286, 1163, 1061, 1018, 913, 807 and 704; δ_H (500 MHz, $CDCl_3$) 0.77 (2 H, br. s, NH_2), 1.47–1.99 (6 H, m, 3 × CH_2), 2.51 (2 H, s, 4-CH_2), 2.74 (1 H, pent, *J* 8.8 Hz, 4-CH), 4.43 and 4.50 (each 1 H, d, *J* 15.9 Hz, PhC*H*CH), 5.29 and 5.41 (each 1 H, s, 2′-H), 5.72 (1 H, s, 5-H), 6.34 (1 H, dd, *J* 3.2, 1.9 Hz, 4″-H), 6.40 (1 H, d, *J* 3.2 Hz, 3″-H) and 7.16–7.34 (6 H, m, ArH); δ_C (125 MHz, $CDCl_3$) 17.2, 23.2, 23.4, 30.6, 39.7, 43.0, 45.9, 69.4, 107.6, 111.8, 114.4, 127.7, 127.8, 128.8, 134.2, 138.7, 142.6, 152.1 and 159.3; *m*/*z* (ES^+) 375 (M^+ + 23, 100%).

(4*RS*,5*SR*)-3-Benzyl-4-cyclobutyl-5-(1-fur-2-ylethenyl)-4-(2-nitrophenylsulfonylamino)methyl-1,3-oxazolidin-2-one (86). 2-Nitrophenylsulfonyl chloride (830 mg, 3.7 mmol) was added to the amine **85** (1.2 g, 3.4 mmol) and triethylamine (0.47 mL) in DCM (7.5 mL) and the solution stirred at rt for 2 h. After concentration under reduced presure, chromatography of the residue (light petroleum to ether) gave the title compound **86** (1.4 g, 76%) as an oil, R_f 0.38 (ether) (Found: M^+ + H, 538.1650. $C_{27}H_{28}N_3O_7S$ requires *M*, 538.1642); ν_{max}/cm^{-1} 3335, 2948, 2359, 1754, 1542, 1402, 1363, 1257, 1176, 1069, 907 and 734; δ_H (500 MHz, $CDCl_3$) 1.50–2.00 (6 H, m, 3 × CH_2), 2.75–2.85 (3 H, m, 4-CH and 4-CH_2), 4.40 and 4.55 (each 1 H, d, *J* 16.5 Hz, PhC*H*CH), 5.15 (1 H, m, NH), 5.34 and 5.47 (each 1 H, s, 2′-H), 5.78 (1 H, s, 5-H), 6.28 and 6.37 (each 1 H, narrow m, 3″-H and 4″-H), 7.15–7.35 (6 H, m, ArH), 7.52 (1 H, m, ArH), 7.55–7.65 (2 H, m, ArH) and 7.72 (1 H, d, *J* 7.0 Hz, ArH); δ_C (75 MHz, $CDCl_3$) 17.2, 23.1, 23.5, 39.9, 45.1, 45.7, 53.7, 67.9, 108.2, 112.0, 115.9, 125.6, 128.0, 129.1, 131.0, 132.9, 133.0, 133.7, 134.0, 138.3, 143.0, 148.0, 151.2 and 158.3; *m*/*z* (ES^+) 560 (M^+ + 23, 100%).

(4*RS*,5*SR*)-3-Benzyl-4-cyclobutyl-5-(1,2-dihydroxy-1-fur-2-ylethyl)-4-(2-nitrophenylsulfonylamino)methyl-1,3-oxazolidin-2-one (87). The alkene **86** (120 mg, 0.33 mmol) was added to osmium tetraoxide (9 mg) and *N*-methylmorpholine-*N*-oxide (118 mg, 1.0 mmol) in water (2.1 mL) and acetone 5.3 mL) and the mixture was stirred at rt for 16 h. An excess of saturated aqueous sodium sulfite was added and the mixture partitioned between water and ethyl acetate. The organic extracts were dried (Na_2SO_4) and concentrated under reduced presure. Chromatography of the residue (light petroleum to ether) gave the title compound **87** (898 mg, 64%) as an oil, R_f 0.27 (ether) (Found: M^+ + Na, 594.1517. $C_{27}H_{29}N_3O_9NaS$ requires *M*, 594.1517); δ_H (500 MHz, DMSO-d_6) 1.80–2.25 (6 H, m, 3 × CH_2), 2.40 (1 H, br. d, *J* 12.0 Hz, 4-*H*CH), 2.82 (1 H, dd, *J* 12.0, 9.0 Hz, 4-HC*H*), 3.05 (1 H, pent, *J* 7.0 Hz, 4-CH), 3.45 (2 H, br. s, 2 × OH), 3.45 and 3.98 (each 1 H, d, *J* 10.0 Hz, 2′-H), 4.18 and 4.54 (each 1 H, d, *J* 15.5 Hz, PhC*H*CH), 4.98 (1 H, s, 5-H), 5.91 and 6.14 (each 1 H, narrow m, 3″-H and 4″-H), 7.03 (2 H, d, *J* 7.0 Hz, ArH), 7.18 (1 H, br. d, *J* 7.0 Hz, ArH), 7.25–7.35 (3 H, m, ArH), 7.40 (1 H, s, 5″-H), 7.75 and 7.94 (each 1 H, t *J* 7.0 Hz, ArH) and 8.12 (1 H, d, *J* 7.2 Hz, ArH); δ_C (100 MHz, DMSO-d_6) 17.1, 22.2, 23.7, 41.4, 43.8, 45.6, 66.0, 66.3, 74.5, 75.8, 107.1, 110.1, 125.0, 127.0, 128.3, 129.5, 130.9, 132.7, 134.4, 138.3, 142.3, 147.1, 153.8 and 156.7; *m*/*z* (ES^+) 594 (M^+ + 23, 100%).

(3a*RS*,6a*RS*)-3-Benzyl-3a-cyclobutyl-6-fur-2-yl-6-hydroxymethyl-5-(2-nitrophenylsulfonyl)hexahydro-2*H*-pyrrolo[3,4-*d*]oxazol-2-one (89). Di-isopropyl diazodicarboxylate (1.8 μL, 9.1 μmol) was

added the diol **87** (4 mg, 7 μmol) and triphenylphosphine (2.5 mg, 9.1 μmol) in tetrahydrofuran (70 μL) at rt and the solution was stirred for 16 h and then concentrated under reduced pressure. Chromatography of the residue (5–10% ether/light petroleum) gave the title compound **89** (3 mg, 75%) as a pale oil, R_f 0.43 (ether) (Found: M^+ + H, 554.1599. $C_{27}H_{28}O_8N_3S$ requires *M*, 554.1592); ν_{max}/cm^{-1} 3343, 2955, 2356, 1742, 1544, 1410, 1360, 1164, 1068, 986, 912, 852 and 734; δ_H (400 MHz, $CDCl_3$) 1.19–1.70 (6 H, m, 3 × CH_2), 2.55 (1 H, m, 3a-CH), 3.79 (1 H, t, *J* 7.5 Hz, OH), 3.63 and 3.85 (each 1 H, d, *J* 11.9 Hz, 4-H), 4.15 (1 H, d, *J* 15.6 Hz, Ph*H*CH), 4.35 and 4.42 (each 1 H, dd, *J* 12.6, 7.3 Hz, 6-*H*CH), 4.43 (1 H, d, *J* 15.6 Hz, PhHC*H*), 5.03 (1 H, s, 6a-H), 6.18 (1 H, dd, *J* 3.3, 1.8 Hz, 4″-H), 6.40 (1 H, dd, *J* 3.5, 0.8 Hz, 3″-H), 7.06 (1 H, dd, *J* 1.8, 0.8 Hz, 5″-H), 7.19–7.29 (5 H, m, ArH), 7.42–7.60 (3 H, m, ArH) and 7.67 (1 H, dd, 8.1, 1.3 Hz, ArH); *m*/*z* (ES^+) 576 (M^+ + 23, 100%) and 554 (M^+ + 1, 70).

(1*RS*,2*RS*,6*SR*)-7-Benzyl-6-cyclobutyl-2-fur-2-yl-2-hydroxy-4-(2-nitrophenylsulfonyl)-4,7-diaza-9-oxabicyclo[4.3.0]nonan-8-one (90). Methanesulfonyl chloride (4.8 μL, 0.063 mmol) was added to the diol **87** (34 mg, 0.06 mmol) in pyridine (0.5 mL) at 0 °C and the reaction mixture was stirred at 0 °C for 2 h. Water (5 mL) was added and the mixture extracted with ethyl acetate (4 × 5 mL). Concentration under reduced pressure gave the mesylate **88** as a pale yellow oil that was immediately dissolved in DMF (0.4 mL) and K_2CO_3 (10 mg, 0.07 mmol) was added. The reaction mixture was warmed to 45 °C for 1.5 h then added to ethyl acetate (10 mL). The organic layer was washed with saturated aqueous $NaHCO_3$ (3 mL) and water (2 × 3 mL) than concentrated under reduced pressure. Chromatography of the residue gave the title compound **90** (14 mg, 42%) as a yellow syrup, R_f 0.58 (ether) (Found: M^+ + H, 554.1586. $C_{27}H_{28}O_8N_3S$ requires *M*, 554.1592); δ_H (400 MHz, $CDCl_3$) 1.41–1.89 (6 H, m, 3 × CH_2), 2.54 (1 H, m, 6-CH), 3.30 (1 H, d, *J* 12.9 Hz, 5-H), 3.49 (1 H, d, *J* 12.6 Hz, 3-H), 3.59 (1 H, d, *J* 12.9 Hz, 5-H′), 3.60 (1 H, dd, *J* 12.6, 1.5 Hz, 3-H′), 3.79 (1 H, d, *J* 1.5 Hz, OH), 4.23 and 4.41 (each 1 H, d, *J* 15.6 Hz, Ph*H*CH), 4.86 (1 H, s, 1-H), 6.24 (1 H, dd, *J* 3.3, 1.8 Hz, 4″-H), 6.39 (1 H, dd, *J* 3.3, 0.8 Hz, 3″-H), 7.19–7.34 (6 H, m, ArH), 7.56–7.68 (3 H, m, ArH) and 7.77 (1 H, m, ArH); δ_C (125 MHz, $CDCl_3$) 17.3, 22.9 (2), 41.1, 45.1, 46.3, 49.1, 64.1, 70.7, 75.0, 108.7, 110.9, 124.4, 128.0, 128.4, 128.7, 130.9, 131.1, 131.9, 134.0, 137.1, 143.0, 148.2, 152.5 and 157.4; *m*/*z* (ES^+) 576 (M^+ + 23, 100%) and 554 (M^+ + 1, 20).

(4*RS*,5*SR*)-3-Benzyl-4-cyclobutyl-5-[1-fur-2-yl-2-(2-trimethylsilylethoxymethoxy)ethyl]-4-hydroxymethyl-1,3-oxazolidin-2-ones (95) and (101). Borane (1 M in THF, 0.54 mL, 0.54 mmol) was added to the alkene **65** (85 mg, 0.18 mmol) in tetrahydrofuran (2.2 mL) at 0 °C. The solution was warmed to 35 °C and stirred for 3 h. Aqueous NaOH (3 M, 0.5 mL) was added and the mixture stirred for 30 min before aqueous hydrogen peroxide (30%, 0.54 mL) was added and the mixture stirred for 30 min. The reaction mixture was poured into water (5 mL) and the aqueous layer extracted with ethyl acetate (3 × 5 mL). The organic extracts were dried (Na_2SO_4) then concentrated under reduced pressure and chromatography of the residue gave the alcohols **78** and **79** (60 mg, 65%), ratio *ca.* 1 : 1, R_f 0.24 (40% ethyl acetate/light petroleum).

Trimethylsilylethoxymethyl chloride (0.8 mL, 4.36 mmol), 4-dimethylaminopyridine (18 mg, 0.015 mmol), tetrabutylammonium iodide (54 mg, 0.015 mmol) and di-isopropylethylamine (1.5 mL, 8.7 mmol) were added to a mixture of the alcohols **78** and **79** (706 mg, 1.45 mmol) in dichloromethane (15 mL) and the mixture was stirred at room temperature for 16 h. Saturated aqueous NH_4Cl (50 mL) was added and the aqueous layer was extracted with ether (3 × 15 mL). The organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue (20% ether/light petroleum) gave the SEM-ethers **93** and **94** (889 mg, 99%) as a yellow oil a *ca.* 1 : 1 mixture, R_f 0.80 (50% ether/light petroleum).

Tetrabutylammonium fluoride (1 M in THF, 0.87 mL, 8.7 mmol) was added to a mixture of the protected diols **93** and **94** (369 mg, 0.58 mmol) in tetrahydrofuran (6 mL) and the solution was stirred for 16 h. Saturated aqueous NH_4Cl (5 mL) was added and the mixture was concentrated under reduced pressure. The mixture was extracted with ether (3 × 5 mL) and the organic extracts were dried (Na_2SO_4). Chromatography of the residue gave gave the title compound **95** (127 mg, 43%) as a yellow oil, R_f 0.84 (ether); ν_{max}/cm^{-1} 3431, 2952, 2351, 1724, 1412, 1249, 1059, 836 and 703; δ_H (500 MHz, $CDCl_3$) 0.00 [9 H, s, $Si(CH_3)_3$], 0.90–0.95 (2 H, m, CH_2Si), 1.06 (1 H, br. s, OH), 1.68–2.03 (6 H, m, 3 × CH_2), 2.96 (1 H, pent, *J* 8.8 Hz, 4-CH), 3.41 (1 H, d, *J* 12.0 Hz, 4-*H*CH), 3.45 (1 H, dd, *J* 9.8, 5.7 Hz, 1′-H), 3.49 (1 H, d, *J* 12.0 Hz, 4-HC*H*), 3.59 (2 H, m, OCH_2CH_2Si), 3.67 (1 H, dd, *J* 9.6, 5.7 Hz, 2′-H), 3.86 (1 H, t, *J* 9.8 Hz, 2′-H′), 4.15 and 4.49 (each 1 H, d, *J* 16.1 Hz, Ph*H*CH), 4.69 (2 H, s, OCH_2O), 5.00 (1 H, s, 5-H), 6.39 (1 H, dd, *J* 2.8, 1.9 Hz, 4″-H), 6.43 (1 H, d, *J* 3.0 Hz, 3″-H), 6.94–6.99 (2 H, m, ArH), 7.17–7.22 (3 H, m, ArH) and 7.33 (1 H, m, 5″-H); δ_C (125 MHz, $CDCl_3$) 0.00, 19.0, 19.5, 24.2, 24.7, 40.1, 41.2, 46.4, 63.6, 66.9, 67.8, 69.9, 76.5, 96.4, 110.5, 112.6, 128.6, 128.7, 130.0, 139.5, 142.9, 152.0 and 159.9; *m*/*z* (ES^+) 524.3 (M^+ + 23, 100%). The second fraction was the title compound **101** (106 mg, 36%) as an oil, R_f 0.53 (ether) (Found: M^+ + Na, 524.2421. $C_{27}H_{39}O_6NSiNa$ requires *M*, 524.2444); ν_{max}/cm^{-1} 3425, 2951, 1739, 1497, 1411, 1360, 1249, 1149, 1064, 917, 860, 835 and 733; δ_H (500 MHz, $CDCl_3$) 0.00 [9 H, s, $Si(CH_3)_3$], 0.86–0.92 (2 H, m, CH_2Si), 1.45–1.85 (7 H, m, 3 × CH_2 and OH), 2.16 (1 H, pent, *J* 9.1 Hz, 4-CH), 3.36 (1 H, dd, *J* 12.8, 2.2 Hz, 4-*H*CH), 3.48 (2 H, t, *J* 8.5 Hz, OCH_2CH_2Si), 3.52 (1 H, dd, *J* 13.0, 6.9 Hz, 4-HC*H*), 3.87–4.01 (3 H, m, 1′-H and 2′-H_2), 4.42 and 4.55 (each 1 H, d, *J* 15.8 Hz, Ph*H*CH), 4.61 and 4.64 (each 1 H, d, *J* 6.8 Hz, O*H*CHO), 4.73 (1 H, d, *J* 10.1 Hz, 5-H), 6.28 (1 H, d, *J* 3.4 Hz, 3″-H), 6.34 (1 H, dd, *J* 3.2, 1.9 Hz, 4″-H), 7.27–7.38 (4 H, m, ArH) and 7.42–7.46 (2 H, m, ArH); δ_C (125 MHz, $CDCl_3$) 0.00, 18.7, 19.4, 23.9, 24.3, 40.0, 40.8, 46.6, 61.5, 66.4, 69.2, 70.2, 78.2, 96.3, 109.9, 112.2, 129.2, 129.3, 130.4, 139.8, 142.8, 154.1 and 160.2; *m*/*z* (ES^+) 524 (M^+ + 23, 100%).

(4*RS*,5*SR*)-3-Benzyl-4-cyclobutyl-5-[(*SR*)-1-fur-2-yl-2-(2-trimethylsilylethoxymethoxy)ethyl]-4-(prop-2-enylaminomethyl)-1,3-oxazolidin-2-one (96). The Dess–Martin periodinane (420 mg,

1 mmol) was added to the alcohol **95** (421 mg, 0.81 mmol) in dichloromethane (8.0 mL) at rt and the reaction mixture was stirred for 2 h. Saturated aqueous $NaHCO_3$ (2 mL) and freshly prepared saturated aqueous $Na_2S_2O_3$ (2 mL) were added and th mixture was stirred for 20 min. Ether (15 mL) was added and the aqueous phase was extracted with ether (4 × 15 mL). The organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure to leave the crude aldehyde. The residue was immediately dissolved in dichloromethane (3.2 mL) and prop-2-enylamine (80 μL, 1.1 mmol) and oven dried $MgSO_4$ (253 mg) were added. The reaction mixture was heated under reflux for 16 h then concentrated under reduced pressure. The residue was immediately dissolved in anhydrous methanol (4.9 mL) and glacial acetic acid (61 μL, 1.1 mmol) and sodium cyanoborohydride (1 M in THF, 1 mL, 1 mmol) were added. The mixture was stirred for 1 h at rt before saturated aqueous $NaHCO_3$ (10 mL) was added and the mixture was extracted with ether (5 × 15 mL). The organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography of the residue (50% ether/light petroleum) gave the title compound **96** (333 mg, 73%), R_f 0.95 (ether) (Found: M^+ + Na, 563.2906. $C_{30}H_{44}O_5N_2NaSi$ requires *M*, 563.2912); ν_{max}/cm^{-1} 3335, 2950, 1752, 1496, 1402, 1249, 1156, 1030, 919, 860, 835 and 759; δ_H (500 MHz, $CDCl_3$) 0.00 [9 H, s, $Si(CH_3)_3$], 0.90–0.95 (2 H, m, CH_2Si), 1.67–2.02 (6 H, m, 3 × CH_2), 2.51 and 2.59 (each 1 H, d, *J* 12.7 Hz, 4-HC*H*), 2.81–2.90 (2 H, m, 4-CH and 1′-H), 2.93 (1 H, dd, *J* 14.2, 6.0 Hz, 1′-H′), 3.56–3.61 (2 H, m, OCH_2CH_2Si), 3.62–3.69 (2 H, m, 1″-H and 2″-H), 3.86 (1 H, m, 2″-H′), 4.17 and 4.45 (each 1 H, d, *J* 16.0 Hz, PhCHCH), 4.69 (2 H, s, OCH_2O), 4.94–5.00 (3 H, m, 5-H and 3′-H_2), 5.63 (1 H, ddt, *J* 17.8, 9.8, 6.0 Hz, 2′-H), 6.36 (1 H, dd, *J* 3.3, 1.6 Hz, 4‴-H), 6.38 (1 H, d, *J* 3.3 Hz, 3‴-H), 6.89–6.93 (2 H, m, ArH), 7.13–7.19 (3 H, m, ArH) and 7.31 (1 H, m, 5‴-H); δ_C (125 MHz, $CDCl_3$) 0.0, 18.8, 19.5, 24.5, 25.0, 40.8, 41.8, 46.4, 51.7, 54.3, 66.8, 67.1, 69.9, 77.2, 96.2, 110.3, 112.5, 117.3, 128.3, 128.5, 129.7, 137.9, 139.6, 142.6, 152.3 and 160.0; *m*/*z* (ES^+) 563 (M^+ + 23, 100%).

(4*RS*,5*SR*)-3-Benzyl-4-cyclobutyl-5-[(*SR*)-1-fur-2-yl-2-(2-(trimethylsilylethoxymethoxy)ethyl]-4-(2-nitrophenylsulfonylaminomethyl)-1,3-oxazolidin-2-one (98). Tetrakistriphenylphosphinepalladium (1 mg, 0.86 μmol) was added to the prop-2-enylamine **96** (41 mg, 0.076 mmol), and 1,3-dimethylbarbituric acid (35 mg, 0.23 mmol) in dichloromethane (0.2 mL) at rt and the mixture was stirred at 35 °C for 2 h. Saturated aqueous $NaHCO_3$ (5 mL) and ether (5 mL) were added and the aqueous layer was extracted with ether (3 × 5 mL). The organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure to give the amine **97** (34 mg, 90%) as a yellow oil, R_f 0.38 (ether) (Found: M^+ + H, 501.2774. $C_{27}H_{41}N_2O_5Si$ requires *M*, 501.2785); ν_{max}/cm^{-1} 2951, 2346, 1749, 1403, 1246, 1155, 1101, 1029 and 835; δ_H (400 MHz, $CDCl_3$) 0.00 (9 H, s, 3 × $SiCH_3$), 0.94 (2 H, m, CH_2Si), 1.55 (2 H, br. s, NH_2), 1.65–2.05 (6 H, m, 3 × CH_2), 1.64 and 1.76 (each 1 H, d, *J* 15.5 Hz, 4-HCH), 2.92 (1 H, pent, *J* 7.0 Hz, 4-CH), 3.54–3.68 (4 H, m, OCH_2CH_2Si, 1′-H and 2′-H), 3.86 (1 H, t, *J* 8.0 Hz, 2′-H′), 4.19 and 4.45 (each 1 H, d, *J* 18.0 Hz, PhCHCH), 4.70 (2 H, s, OCH_2O), 4.97 (1 H, s, 5-H), 6.37 and 6.41 (each 1 H, narrow m, 3″-H and 4″-H), 6.94 (2 H, m, ArH), 7.12–7.20 (3 H, m, ArH) and 7.32 (1 H, s, ArH); δ_C (100 MHz, $CDCl_3$) 0.00, 19.0, 19.5, 24.5, 25.0, 41.0, 41.5, 44.6, 46.3, 66.8, 67.8, 70.0, 77.4, 96.3, 110.5, 112.6, 128.5, 129.8, 139.6, 142.7, 152.2 and 160.1; *m*/*z* (ES^+) 523 (M^+ + 23, 95%) and 501 (M^+ + 1, 55).

This amine **97** was immediately taken up in dichloromethane (0.2 mL) and 2-nitrobenzenesulfonyl chloride (17 mg, 74 μmol) and triethylamine (10 μL, 68 μmol) were added. The solution was stirred at rt for 2 h, saturated aqueous NH_4Cl (5 mL) was added and the mixture was extracted with ether (4 × 5 mL). The organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue (light petroleum to neat ether) gave the title compound **98** (28 mg, 60%) as a clear oil, R_f 0.7 (ether) (Found: M^+ + Na, 708.2384. $C_{33}H_{43}O_9N_3NaSSi$ requires *M*, 708.2381); ν_{max}/cm^{-1} 3323, 2950, 1747, 1541, 1409, 1361, 1249, 1175, 1059, 836 and 733; δ_H (400 MHz, $CDCl_3$) 0.00 [9 H, s, $Si(CH_3)_3$], 0.89–0.97 (2 H, m, CH_2Si), 1.72–2.14 (6 H, m, 3 × CH_2), 2.80 (1 H, dd, *J* 13.6, 5.2 Hz, 4-HCH), 2.85 (1 H, dd, *J* 13.6, 6.6 Hz, 4-HCH), 2.99 (1 H, pent, *J* 8.4 Hz, 4-CH), 3.39 (1 H, ddd, *J* 10.2, 5.4 Hz, 0.9 Hz, 1′-H), 3.58–3.63 (2 H, m, OCH_2CH_2Si), 3.65 (1 H, dd, *J* 9.8, 5.5 Hz, 2′-H), 3.87 (1 H, t, *J* 9.9 Hz, 2′-H′), 3.96 and 4.54 (each 1 H, d, *J* 16.1 Hz, PhCHCH), 4.70 (2 H, s, OCH_2O), 5.07 (1 H, d, *J* 1.1 Hz, 5-H), 5.12 (1 H, br. t, *J* 6.1, NH), 6.33 (1 H, dd, *J* 3.3, 1.8 Hz, 4″-H), 6.40 (1 H, dd, *J* 3.3, 0.7 Hz, 3″-H), 6.90–6.94 (2 H, m, ArH), 7.13 (1 H, dd, *J* 1.8, 0.7 Hz, 5″-H), 7.14–7.19 (3 H, m, ArH), 7.58–7.72 (3 H, m, ArH) and 7.79 (1 H, dd, *J* 8.0, 1.3 Hz, ArH); δ_C (125 MHz, $CDCl_3$) 0.00, 18.9, 19.5, 24.2, 24.9, 40.9, 41.3, 46.2, 46.8, 66.8, 67.0, 69.6, 76.3, 96.4, 111.0, 112.8, 126.7, 128.7, 128.9, 130.1, 132.6, 133.8, 134.0, 135.2, 139.1, 142.9, 149.4, 151.1 and 159.2; *m*/*z* (ES^+) 708 (M^+ + 23, 100%).

(4*RS*,5*SR*)-3-Benzyl-4-cyclobutyl-5-[(*SR*)-1-fur-2-yl-2-hydroxyethyl]-4-(2-nitrophenylsulfonylaminomethyl)-1,3-oxazolidin-2-one (99). Nitromethane (162 μL, 02.9 mmol) and $MgBr_2$ (270 mg, 1.45 mmol) were added to the SEM-ether **98** (72 mg, 0.1 mmol) in anhydrous ether 24 mL) and the reaction mixture was stirred at rt for 2 h before dichloromethane (10 mL) and water (10 mL) were added. The aqueous layer was extracted with dichloromethane (4 × 10 mL), and the organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Filtration through a short pad of silica gave the title compound **99** (45 mg, 77%) as a clear oil, R_f 0.3 (ether) (Found: M^+ + Na, 578.1566. $C_{27}H_{29}O_8N_3NaS$ requires *M*, 578.1568); δ_H (400 MHz, $CDCl_3$) 1.79–2.24 (6 H, m, 3 × CH_2), 2.90 (1 H, dd, *J* 13.6, 6.3 Hz 4-HCH), 2.99 (1 H, dd, *J* 13.6, 8.1 Hz, 4-HCH), 3.09 (1 H, m, 4-CH), 3.44 (1 H, ddd, *J* 9.3, 5.8, 1.3 Hz, 1′-H), 3.94 and 4.07 (each 1 H, m, 2′-H), 4.07 and 4.64 (each 1 H, d, *J* 16.1 Hz, PhCHCH), 5.20 (1 H, t, *J* 6.1 Hz, NH), 5.22 (1 H, d, *J* 1.3 Hz, 5-H), 6.46 (1 H, dd, *J* 3.3, 2.0 Hz, 4″-H), 6.52 (1 H, dd, *J* 3.3, 0.7 Hz, 3″-H), 7.01–7.05 (2 H, m, ArH), 7.24–7.31 (4 H, m, ArH), 7.71–7.84 (3 H, m, ArH) and 7.91 (1 H, dd, *J* 8.0, 1.3 Hz, ArH); δ_C (125 MHz, $CDCl_3$) 17.4, 22.8, 23.6, 39.4, 41.9, 44.8, 45.3, 63.5, 65.5, 74.9, 109.6, 111.5, 125.2, 127.1, 127.5, 128.9, 131.2, 132.5, 133.0, 134.4, 137.8, 141.7, 148.1, 150.2 and 158.2; *m*/*z* (ES^+) 578 (M^+ + 23, 100%).

1*RS*,2*SR*,6*SR*)-7-Benzyl-6-cyclobutyl-2-fur-2-yl-4-(2-nitrophenylsulfonyl)-4,7-diaza-9-oxabicyclo[4.3.0]nonan-8-one (91). Triphenylphosphine (19 mg, 72 μmol) and di-isopropyl azodicarboxylate (14 μL, 72 μmol) were added to the sulfonamide **99** (31 mg, 55 μmol) in tetrahydrofuran (0.5 mL) at rt and the reaction mixture was stirred for 2 h before concentration under reduced pressure. Chromatography of the residue (light petroleum to 50% ether/light petroleum) gave the title compound **91** (22 mg, 73%) as a pale oil (Found: M^+ + 1, 538.1637. $C_{27}H_{28}O_7N_3S$ requires *M*, 538.1642); ν_{max}/cm^{-1} 2919, 1744, 1543, 1459, 1406, 1360, 1166, 1061, 909, 852 and 733; δ_H (500 MHz, $CDCl_3$) 1.29–1.76 (6 H, m, 3 × CH_2), 2.22 (1 H, m, 6-CH), 3.04 (1 H, d, *J* 14.2 Hz, 5-H), 3.33–3.41 (2 H, m, 2-H and 3-H), 3.63 (1 H, d, *J* 14.2 Hz, 5-H′), 3.69 (1 H, m, 3-H′), 4.10 and 4.62 (each 1 H, d, *J* 15.5 Hz, PhC*H*CH), 4.79 (1 H, d, *J* 6.0 Hz, 1-H), 6.10 (1 H, d, *J* 3.2 Hz, 3″-H), 6.23 (1 H, dd, *J* 3.2, 1.9 Hz, 4″-H), 7.20–7.29 (4 H, m, ArH), 7.32–7.36 (2 H, m, ArH), 7.59–7.71 (3 H, m, ArH) and 7.90 (1 H, dd, *J* 7.6, 1.6 Hz, ArH); *m*/*z* (ES^+) 555.4 (M^+ + 18, 100%).

Triethylsilane (9 μL, 60 μmol) and boron trifluoride diethyl etherate (8.3 μL, 65 μmol) were added to the tertiary alcohol **90** (13 mg, 23 μmol) in dichloromethane (0.2 ml) at 0 °C and the reaction mixture stirred at 0 °C for 15 min and at rt for 2 h. Saturated aqueous $NaHCO_3$ (5 mL) was added and the aqueous mixture extracted with dichloromethane (3 × 5 mL). The organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography as before gave the title compound **91** (4 mg, 32%), R_f 0.53 (ether).

1*RS*,2*SR*,6*SR*)-7-Benzyl-6-cyclobutyl-2-fur-2-yl-4,7-diaza-9-oxabicyclo[4.3.0]nonan-8-one (100). Potassium carbonate (48 mg) and thiophenol (27 μL, 26.2 μmol) were addded to the sufonamide **91** (47 mg, 87 μmol) in acetonitrile (1.75 mL) and the mixture stirred at rt for 2 h. After concentration under reduced pressure, chromatography of the residue (light petroleum to 10% methanol in ether) gave the title compound **100** (24 mg, 75%) as an oil, R_f 0.16 (ether) (Found: M^+ + H, 353.1851. $C_{21}H_{25}N_2O_3$ requires *M*, 353.1860); δ_H (400 MHz, $CDCl_3$) 1.65–1.99 (6 H, m, 3 × CH_2), 2.45 (1 H, dd, *J* 2.0, 14.0 Hz, 3-H), 2.47 (1 H, d, *J* 16.2 Hz, 5-H), 2.50 (1 H, m, 6-CH), 2.75 (1 H, m, 2-H), 2.90 (1 H, dd, *J* 1.5, 16.2 Hz, 5-H′), 3.00 (1 H, ddd, *J* 1.0, 6.5 and 16.0 Hz, 3-H′), 4.00 (1 H, d, *J* 15.4 Hz, PhC*H*CH), 4.60 (1 H, d, *J* 8.6 Hz, 1-H), 4.71 (1 H, d, *J* 15.4 Hz, PhHC*H*), 6.14 (1 H, d, *J* 4.1 Hz, 3′-H), 6.26 (1 H, dd, *J* 2.0, 4.1 Hz, 4′-H), and 7.20–7.37 (6 H, m, ArH); *m*/*z* (ES^+) 353.1 (M^+ + 1, 100%).

(4*RS*,5*SR*)-3-Benzyl-4-cyclobutyl-5-[(*RS*)-1-fur-2-yl-2-(2-(trimethylsilylethoxymethoxy)ethyl]-4-(prop-2-enylaminomethyl)-1,3-oxazolidin-2-one (102). The Dess–Martin periodinane (185 mg, 0.44 mmol) was added to the alcohol **101** (189 mg, 0.365 mmol) in dichloromethane (3.6 mL) at rt and the reaction mixture was stirred for 2 h. Saturated aqueous $NaHCO_3$ (1 mL) and freshly prepared saturated aqueous $Na_2S_2O_3$ (1 mL) were added and the stirring was continued for 20 min. Ether (5 mL) was added and the aqueous layer was extracted with ether (4 × 5 mL). The organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure to leave the crude aldehyde. The residue was immediately dissolved in DCM (1.5 ml) and prop-2-enylamine (35 μL, 0.48 mmol) and oven dried $MgSO_4$ (114 mg) were added. The reaction mixture was heated under reflux for 16 h and concentrated under reduced pressure. The residue was immediately dissolved in anhydrous methanol (2.2 mL) and glacial acetic acid (27 μL, 0.48 mmol) and sodium cyanoborohydride (1 M in THF, 0.44 mL, 0.44 mmol) were added at rt. The reaction mixture was stirred for 1 h before saturated aqueous $NaHCO_3$ (5 mL) was added. The aqueous mixture was extracted with ether (5 × 5 mL) and the organic extracts were dried (Na_2SO_4). After concentration under reduced pressure, chromatography of the residue (50% ether/light petroleum) gave the title compound **102** (137 mg, 70%) as an oil, R_f 0.27 (50% ether/light petroleum) (Found: M^+ + H, 541.3089. $C_{30}H_{45}O_5N_2Si$ requires *M*, 541.3092); ν_{max}/cm^{-1} 2952, 1744, 1408, 1248, 1111, 1062, 1034, 835 and 708; δ_H (500 MHz, $CDCl_3$) 0.00 [9 H, s, $Si(CH_3)_3$], 0.86–0.92 (2 H, m, CH_2Si), 1.38–1.83 (6 H, m, 3 × CH_2), 2.17 (1 H, pent, *J* 8.7, 4-CH), 2.46 and 2.54 (each 1 H, d, *J* 13.6 Hz, 4-*H*CH), 2.83 (1 H, dd, *J* 13.9, 6.3 Hz, 1′-H), 2.90 (1 H, dd, *J* 13.9, 6.0 Hz, 1′-H′), 3.47 (2 H, t, *J* 8.5 Hz, OCH_2CH_2Si), 3.94 (1 H, dd, *J* 9.5, 3.9 Hz, 2″-H), 3.97 (1 H, dd, *J* 9.5, 7.3 Hz, 2″-H′), 4.19 (1 H, ddd, *J* 11.0, 7.3, 4.0 Hz, 1″-H), 4.39 and 4.46 (each 1 H, d, *J* 15.8 Hz, PhC*H*CH), 4.60 and 4.63 (each 1 H, d, *J* 6.8 Hz, OHCHO), 4.65 (1 H, d, *J* 11.0 Hz, 5-H), 5.02 (1 H, d, *J* 10.1 Hz, 3′-H), 5.03 (1 H, d, *J* 17.6 Hz, 3′-H′), 5.66 (1 H, ddt, *J* 17.6, 10.1, 6.3 Hz, 2′-H), 6.22 (1 H, dd, *J* 3.2 Hz, 3‴-H), 6.32 (1 H, dd, *J* 3.2, 1.8 Hz, 4‴-H), 7.26–7.36 (4 H, m, ArH) and 7.42–7.45 (2 H, m, ArH); δ_C (125 MHz, $CDCl_3$) 0.0, 2.4, 18.3, 19.4, 24.0, 24.4, 40.4, 41.8, 46.6, 49.8, 53.7, 66.3, 69.3, 78.2, 96.3, 110.0, 112.1, 117.5, 129.1, 129.5, 130.1, 138.0, 139.7, 142.6, 154.4 and 160.0; *m*/*z* (ES^+) 541.6 (M^+ + 1, 100%).

(4*RS*,5*SR*)-3-Benzyl-4-cyclobutyl-5-[(*RS*)-1-fur-2-yl-2-(2-(trimethylsilylethoxymethoxy)ethyl]-4-(2-nitrophenylsulfonylaminomethyl)-1,3-oxazolidin-2-one (104). Tetrakistriphenylphosphinepalladium (0.5 mg, 0.45 μmol) was added to the propenylamine **102** (22 mg, 0.04 mmol), and 1,3-dimethylbarbituric acid (19 mg, 0.12 mmol) in dichloromethane (0.1 mL) at rt and the mixture was stirred at 35 °C for 2 h. Saturated aqueous $NaHCO_3$ (5 mL) and ether (5 mL) were added and the aqueous layer was extracted with ether (3 × 5 mL). The organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure to give the amine **103** (16 mg, 79%) as a yellow oil, R_f 0.24 (ether) (Found: M^+ + H, 501.2777. $C_{27}H_{41}N_2O_5Si$ requires *M*, 501.2779); ν_{max}/cm^{-1} 3385, 2951, 2358, 1742, 1408, 1249, 1150, 1110, 1062, 835 and 709; δ_H (400 MHz, $CDCl_3$) 0.00 (9 H, s, 3 × $SiCH_3$), 0.80–0.95 (2 H, m, CH_2Si), 1.28–1.78 (6 H, m, 3 × CH_2), 2.05 (1 H, pent, *J* 7.0 Hz, 4-CH), 2.71 and 2.79 (each 1 H, d, *J* 14.0 Hz, 4-*H*CH), 3.45–3.55 (2 H, m, OCH_2CH_2Si), 3.90–4.00 (3 H, m, 1′-H and 2′-H_2), 4.35 (1 H, d, *J* 15.0 Hz, PhC*H*CH), 4.50–4.65 (4 H, m, 5-H, PhHC*H* and OCH_2O), 6.27 and 6.35 (each 1 H, narrow m, 3″-H and 4″-H), 7.25–7.58 (5 H, m, ArH) and 7.69 (1 H, m, ArH); δ_C (100 MHz, $CDCl_3$) 0.00, 18.2, 19.4, 24.2, 24.4, 40.7, 41.1, 42.4, 46.8, 66.4, 69.4, 70.3, 96.3, 109.7, 112.2, 128.9, 129.3, 130.0, 142.7, 154.1 and 160.5; *m*/*z* (ES^+) 501.5 (M^+ + 1, 100%).

This amine **103** was immediately taken up in dichloromethane (0.1 mL) and 2-nitrobenzenesulfonyl chloride (8 mg, 0.035 mmol) and triethylamine (4.5 μL, 0.032 mmol) were added. The solution was stirred at rt for 2 h, saturated aqueous NH_4Cl (5 mL) was added and the mixture was extracted with ether (4 × 5 mL). The organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue (light petroleum to neat ether) gave title compound **104** (15 mg, 70%) as a white foam, R_f 0.65 (ether) (Found: M^+ + Na, 708.2389. $C_{33}H_{43}O_9N_3NaSSi$ requires *M*, 708.2381); ν_{max}/cm^{-1} 2949, 1747, 1542, 1405, 1360, 1248, 1173, 1111, 1063, 917, 853, 836 and 733; δ_H (500 MHz, $CDCl_3$) 0.00 [9 H, s, Si$(CH_3)_3$], 0.87–0.92 (2 H, m, CH_2Si), 1.31–1.84 (6 H, m, 3 × CH_2), 2.19 (1 H, pent, *J* 9.1 Hz, 4-CH), 3.02 (1 H, dd, *J* 14.2, 6.0 Hz, 4-HC*H*), 3.27 (1 H, dd, *J* 14.0, 6.9 Hz, 4-*H*CH), 3.48–3.53 (2 H, m, OCH_2CH_2Si), 3.56 (1 H, ddd, *J* 10.4, 6.3, 4.4 Hz, 1′-H), 3.91 (1 H, dd, *J* 9.6, 4.4 Hz, 2′-H), 3.96 (1 H, dd, *J* 9.6, 6.6 Hz, 2′-H′), 4.24 and 4.58 (each 1 H, d, *J* 16.1 Hz, Ph*H*CH), 4.63 and 4.66 (each 1 H, d, *J* 6.8 Hz, OHC*H*O), 4.77 (1 H, d, *J* 10.1 Hz, 5-H), 5.43 (1 H, br. t, *J* 6.2 Hz, NH), 6.29 (1 H, d, *J* 3.2 Hz, 3″-H), 6.34 (1 H, dd, *J* 3.2, 1.9 Hz, 4″-H), 7.23–7.35 (6 H, m, ArH), 7.72–7.79 (2 H, m, ArH), 7.85 (1 H, dd, *J* 7.6, 1.6 Hz, ArH) and 7.95 (1 H, dd, *J* 7.3, 1.6 Hz, ArH); δ_C (125 MHz, $CDCl_3$) 0.0, 18.0, 19.4, 24.0, 24.1, 40.3, 40.7, 44.5, 46.7, 66.6, 68.8, 78.0, 96.3, 110.0, 112.5, 126.8, 129.0, 129.1, 130.2, 132.4, 134.1, 134.2, 135.3, 139.2, 143.1, 149.5, 153.1 and 159.3; *m*/*z* (ES^+) 708.4 (M^+ + 23, 100%).

(4*RS*,5*SR*)-3-Benzyl-4-cyclobutyl-5-[(*RS*)-1-fur-2-yl-2-hydroxyethyl]-4-(2-nitrophenylsulfonylaminomethyl)-1,3-oxazolidin-2-one (105). Nitromethane (34 μL, 0.61 mmol) and $MgBr_2$ (56 mg, 0.3 mmol) were added to the SEM-ether **104** (15 mg, 21 μmol) in anhydrous ether (0.4 mL) and the reaction mixture was stirred at rt for 2 h before dichloromethane (5 mL) and water (5 mL) were added. The aqueous layer was extracted with dichloromethane (4 × 5 mL), and the organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Filtration through a short pad of silica gave the title compound **105** (9 mg, 75%) as a pale yellow oil, R_f 0.16 (ether) (Found: M^+ + Na, 578.1580. $C_{27}H_{29}O_8N_3NaS$ requires *M*, 578.1568); ν_{max}/cm^{-1} 3336, 2915, 1739, 1541, 1410, 1360, 1171, 1067, 911, 853 and 731; δ_H (500 MHz, $CDCl_3$) 1.22–1.76 (6 H, m, 3 × CH_2), 2.09 (1 H, pent, *J* 8.6 Hz, 4-CH), 2.97 and 3.22 (each 1 H, d, *J* 13.9 Hz, 4-*H*CH), 3.49 (1 H, dt, *J* 10.4, 5.4 Hz, 1′-H), 3.95 (2 H, m, 2′-H_2), 4.18 and 4.52 (each 1 H, d, *J* 16.1 Hz, Ph*H*CH), 5.75 (1 H, d, *J* 10.4 Hz, 5-H), 5.42 (1 H, br. s, NH), 6.26 (1 H, d, *J* 3.3 Hz, 3″-H), 6.30 (1 H, dd, *J* 3.3, 2.2 Hz, 4″-H), 7.16–7.30 (6 H, m, ArH), 7.64–7.72 (2 H, m, ArH), 7.78 (1 H, dd, *J* 7.9, 0.9 Hz, ArH) and 7.88 (1 H, dd, *J* 7.6, 1.2 Hz, ArH); δ_C (125 MHz, $CDCl_3$) 15.3, 16.6, 22.7, 38.9, 41.1, 43.0, 45.4, 63.7, 65.9, 67.5, 109.0, 111.1, 125.4, 127.6, 127.8, 128.9, 131.0, 132.8(2), 134.0, 137.7, 142.3, 148.1, 151.3 and 157.9; *m*/*z* (ES^+) 573.4 (M^+ + 18, 100%).

(1*RS*,2*RS*,6*SR*)-7-Benzyl-6-cyclobutyl-2-fur-2-yl-4-(2-nitrophenylsulfonyl)-4,7-diaza-9-oxabicyclo[4.3.0]nonan-8-one (106). Triphenylphosphine (5.5 mg, 21 μmol) and di-isopropyl azodicarboxylate (4 μL, 21 μmol) were added to the sulfonamide **105** (9 mg, 16 μmol) in tetrahydrofuran (0.16 mL) at rt and the reaction mixture was stirred for 2 h. After concentration under reduced pressure, chromatography of the residue (light petroleum to 50% ether/light petroleum) gave the title compound **106** (7 mg, 80%) as a pale oil, that crystallised from ether on standing, R_f 0.48 (ether) (Found: M^+ + Na, 560.1454. $C_{27}H_{27}O_7N_3NaS$ requires *M*, 560.1462); δ_H (500 MHz, $CDCl_3$) 1.04–1.89 (6 H, m, 3 × CH_2), 2.50 (1 H, pent, *J* 8.8 Hz, 6-CH), 3.25 (1 H, d, *J* 14.5 Hz, 5-H), 3.38 (1 H, dd, *J* 12.3, 5.7 Hz, 2-H), 3.55 (1 H, dd, *J* 10.7, 5.9 Hz, 3-H), 3.66 (1 H, t, *J* 11.0 Hz, 3-H′), 3.68 (1 H, d, *J* 14.6 Hz, 5-H′), 3.95 and 4.75 (each 1 H, d, *J* 16.1 Hz, Ph*H*CH), 4.85 (1 H, s, 1-H), 6.37 (1 H, m, 4′-H), 6.39 (1 H, d, *J* 3.2 Hz, 3′-H), 7.25–7.39 (6 H, m, ArH), 7.66–7.77 (3 H, m, ArH) and 8.00 (1 H, d, *J* 7.4 Hz, ArH); *m*/*z* (ES^+) 560.4 (M^+ + 23, 100%).

(1*RS*,2*RS*,6*SR*)-7-Benzyl-6-cyclobutyl-2-fur-2-yl-4,7-diaza-9-oxabicyclo[4.3.0]nonan-8-one (64). Potassium carbonate (45 mg,) and thiophenol (25 μl, 245 μmol) were added to the sulfonamide **106** (44 mg, 82 μmol) in acetonitrile (1.7 mL) and the reaction mixture stirred at rt for 2 h. After concentration under reduced pressure, chromatography of the residue (light petroleum to 10% methanol/ether) gave the title compound **64** (25 mg, 86%) as a pale oil, R_f 0.38 (10% methanol/ether) (Found: M^+ + H, 353.1861. $C_{21}H_{25}O_3N_2$ requires *M*, 353.1860); ν_{max}/cm^{-1} 3354, 2931, 1742, 1409, 1164, 1014 and 705; δ_H (500 MHz, $CDCl_3$) 1.52–1.95 (6 H, m, 3 × CH_2), 2.34 (1 H, d, *J* 14.5 Hz, 5-H), 2.62 (1 H, pent, *J* 8.8 Hz, 6-CH), 2.64 (1 H, d, *J* 14.5 Hz, 5-H′), 3.02 (1 H, t, *J* 12.0 Hz, 3-H), 3.12 (1 H, dd, *J* 12.0, 6.3 Hz, 3-H′), 3.16 (1 H, ddd, *J* 12.0, 6.3, 2 Hz, 2-H), 4.14 and 4.41 (each 1 H, d, *J* 15.5 Hz, Ph*H*CH), 4.78 (1 H, d, *J* 2 Hz, 1-H), 6.19 (1 H, d, *J* 3.2 Hz, 3″-H), 6.27 (1 H, dd, *J* 3.2, 2.0 Hz, 4″-H) and 7.18–7.34 (6 H, m, ArH); δ_C (125 MHz, $CDCl_3$) 17.6, 22.3, 22.9, 35.5, 38.4, 41.7, 44.7, 64.0, 65.9, 74.9, 106.9, 110.5, 130.0, 128.8, 138.2, 141.6, 152.2 and 158.7; *m*/*z* (ES^+) 353.3 (M^+ + 1, 100%).

(4*SR*,5*RS*)-3-Benzyl-4-(*tert*-butyldimethylsilyloxymethyl)-4-cyclobutyl-5-[1-(2-phenyl-1,3-ozaxol-5-yl)prop-2-en-2-yl]-1,3-oxazolidin-2-one (108). *n*-Butyllithium (2.5 M in THF, 2.8 mL, 6.96 mmol, 3 eq.) was added to 5-bromo-2-phenyloxazole (1.6 g, 6.96 mmol, 3 eq.) in THF (8 mL) at −18 °C and the resulting suspension was stirred for 45 min, cooled to −40 °C and added to a suspension of CuCN (596 mg, 6.96 mmol, 3 eq.) and LiCl (590 mg, 13.92 mmol, 6 eq.) in THF (8 mL). The reaction mixture was stirred at −40 °C for 1 h and then the bromide **43** (1.15 g, 2.32 mmol) in THF (8 mL) was added. The mixture stirred for 18 h, warmed to rt, diluted with ether (15 mL) and saturated aqueous ammonium chloride (15 mL) was added. The aqueous phase was extracted with ether (3 × 20 mL) and the organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography (ethyl acetate : light petroleum = 1 : 25) of the residue gave the title compound **108** (1.04 g, 80%) as a colourless oil, R_f = 0.11 (ethyl acetate : light petroleum = 1 : 10) (Found: M^+ + H, 559.2986. $C_{33}H_{43}N_2O_4Si$ requires *M*, 559.2993); ν_{max}/cm^{-1} 3087, 3064, 3033, 2953, 2930, 2898, 2857, 1754, 1648, 1600, 1549, 1486, 1470, 1401, 1355, 1291, 1256, 1200, 1161, 1104, 1043, 1005, 915, 840 and 777; δ_H (400 MHz, $CDCl_3$) 0.00 and 0.03 (each

3 H, s, $SiCH_3$), 0.88 [9 H, s, $SiC(CH_3)_3$], 1.56–2.07 (6 H, m, 3 × CH_2), 2.92 (1 H, pent, *J* 9.0 Hz, 4-CH), 3.55 (1 H, d, *J* 11.0 Hz, 4-HC*H*), 3.57 (1 H, d, *J* 17.5 Hz, 1′-H), 3.62 (1 H, *J* 11.0 Hz, 4-HC*H*), 3.69 (1 H, d, *J* 17.5 Hz, 1′-H′), 4.40 and 4.64 (each 1 H, d, *J* 15.7 Hz, PhHC*H*), 4.96 (1 H, s, 5-H), 5.09 and 5.32 (each 1 H, s, 3′-H), 7.24–7.40 (6 H, m, 4″-H, ArH), 7.44–7.59 (3 H, m, ArH) and 7.98–8.02 (2 H, m, ArH); δ_C (100 MHz, $CDCl_3$) −5.9, −5.6, 17.0, 18.1, 22.8, 23.3, 25.8, 28.1, 38.3, 46.0, 62.6, 68.2, 79.3, 115.6, 117.3, 126.2, 126.4, 127.4, 127.5, 128.5, 128.8, 130.9, 138.4, 138.8, 145.7, 158.7 and 161.1; *m*/*z* (CI^+) 559 (M^+ + 1, 1%) and 106 (100).

(4*SR*,5*RS*)-3-Benzyl-4-(*tert*-butyldimethylsilyloxymethyl)-4-cyclobutyl-5-[(*RS*)-1-(2-phenyl-1,3-oxazol-5-yl)-3-hydroxyprop-2-yl]-1,3-oxazolidin-2-one (109). Borane (1 M in THF, 18.6 mL, 18.6 mmol, 10 eq.) was added dropwise to the alkene **108** (1.04 g, 1.84 mmol) in THF (18 mL) at 0 °C and the mixture was warmed to rt then stirred for 24 h. Ethanol (16.25 mL), saturated sodium acetate (51.5 mL) and hydrogen peroxide (30% in water, 18 mL) were added dropwise and the reaction mixture was heated under reflux for 1.5 h. After cooling to rt, the aqueous phase was extracted with ether (3 × 100 mL), and the organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography (ethyl acetate : light petroleum = 1 : 2 to 1 : 1) of the residue gave the title compound **109** (532 mg, 50%) containing small amounts of its 2′-epimer, R_f = 0.30 (ethyl acetate : light petroleum = 1 : 2) (Found: M^+ + H, 577.3098. $C_{33}H_{45}N_2O_5Si$ requires *M*, 577.3098); ν_{max}/cm^{-1} 3414, 3065, 3032, 2951, 2932, 2892, 2859, 1732, 1602, 1550, 1492, 1408, 1357, 1295, 1255, 1172, 1112, 1069, 1032, 983, 913, 840 and 778; δ_H (300 MHz, $CDCl_3$) 0.04 and 0.05 (each 3 H, s, $SiCH_3$), 0.86 [9 H, s, $SiC(CH_3)_3$], 1.24–1.98 (6 H, m, 3 × CH_2), 2.10 (1 H, br. s, OH), 2.49–2.61 (2 H, m, 4-CH, 2′-H), 2.93 (1 H, dd, *J* 7.0, 15.2 Hz, 1′-H), 3.13 (1 H, dd, *J* 7.2, 15.2 Hz, 1′-H′), 3.65 and 3.71 (each 1 H, d, *J* 11.2 Hz, 4-HC*H*), 3.80 (1 H, dd, *J* 3.0, 11.2 Hz, 3′-H), 3.99 (1 H, dd, *J* 4.2, 11.2 Hz, 3′-H′), 4.21 (1 H, *J* 16.0 Hz, PhHC*H*), 4.43 (1 H, d, *J* 5.2 Hz, 5-H), 4.62 (1 H, *J* 16.0 Hz, PhHC*H*), 7.00 (1 H, s, 4″-H), 7.24–7.38 (5 H, m, ArH), 7.42–7.47 (3 H, m, ArH) and 7.95–8.01 (2 H, m, ArH); δ_C (75 MHz, $CDCl_3$) −5.9, −5.8, 17.1, 17.9, 23.2, 23.4, 25.7, 26.1, 39.1, 39.4, 45.9, 61.4, 61.6, 68.4, 78.8, 125.9, 126.0, 127.4(2), 127.6, 128.5, 128.7, 130.2, 138.3, 150.0, 158.9 and 161.3; *m*/*z* (CI^+) 577 (M^+ + 1, 1%) and 391 (100).

(4*SR*,5*RS*)-3-Benzyl-4-cyclobutyl-4-(hydroxymethyl)-5-[(*RS*)-1-(2-phenyl-1,3-oxazol-5-yl)-3-hydroxyprop-2-yl]-1,3-oxazolidin-2-one (110). Following the procedure for the preparation of compound **82**, the silyl ether **109** (532 mg, 0.92 mmol), after stirring for 1 h and chromatography (ethyl acetate : light petroleum = 1 : 2 to neat ethyl acetate), gave the title compound **110** (352 mg, 83%), R_f = 0.18 (ethyl acetate : light petroleum = 3 : 2) (Found: M^+ + H, 463.2225. $C_{27}H_{31}N_2O_5$ requires *M*, 463.2234); ν_{max}/cm^{-1} 3387, 3064, 3032, 2942, 2871, 1727, 1600, 1550, 1486, 1433, 1413, 1357, 1294, 1258, 1164, 1069, 982 and 912; δ_H (300 MHz, $CDCl_3$) 1.24–1.85 (6 H, m, 3 × CH_2), 2.39 (1 H, pent, *J* 8.5 Hz, 4-CH), 2.61 (1 H, m, 2′-H), 2.86 (1 H, dd, *J* 7.7, 15.2 Hz, 1′-H), 3.03 (1 H, dd, *J* 6.2, 15.2 Hz, 1′-H′), 3.61 and 3.71 (each 1 H, d, *J* 13.0 Hz, 4-HC*H*), 3.82 (1 H, dd, *J* 4.2, 11.0 Hz, 3′-H), 3.96 (1 H, dd, *J* 6.2, 11.0 Hz, 3′-H′), 4.31 (1 H, *J* 16.0 Hz, PhHC*H*), 4.51 (1 H, d, *J* 3.5 Hz, 5-H), 4.58 (1 H, d, *J* 16.0 Hz, PhHC*H*), 7.00 (1 H, s, 4″-H), 7.25–7.46 (8 H, m, ArH) and 7.95–7.99 (2 H, m, ArH); δ_C (75 MHz, $CDCl_3$) 17.2, 22.9, 23.0, 27.5, 39.2, 39.3, 45.4, 60.1, 61.5, 68.8, 78.8, 125.8, 126.0, 127.2, 127.6, 127.7, 128.7, 128.8, 130.3, 138.1, 149.9, 159.4 and 161.4; *m*/*z* (CI^+) 463 (M^+ + 1, 100%).

(1*RS*,2*RS*,6*SR*)-4,7-Bis-benzyl-6-cyclobutyl-2-(2-phenyl-1,3-oxazol-5-yl)methyl-4,7-diaza-9-oxabicyclo[4.3.0]nonan-8-one (112). Freshly distilled methane sulfonyl chloride (0.235 mL, 3.03 mmol, 4 eq.) and triethylamine (0.528 mL, 3.78 mmol, 5 eq.) were added successively to the diol **110** (350 mg, 0.757 mmol) in DCM (15 mL) at 0 °C and the reaction mixture was allowed to warm to rt and was stirred for 1 h. Saturated aqueous ammonium choride (15 mL) and ether (15 mL) were added and the aqueous phase was extracted with ether (3 × 20 mL). The organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure to leave the bis-mesylate **111** that was dissolved in benzylamine (25 mL) and the solution heated at 90 °C for 18 h. The reaction mixture was allowed to cool to rt and the excess benzylamine was distilled off under reduced pressure. Chromatography (ethyl acetate : light petroleum = 1 : 20 to 1 : 10 with 1% methanol) of the residue gave the piperidine **112** (327 mg, 81%) containing about 10% of its 2-epimer. Repeated chromatography (ethyl acetate : light petroleum = 1 : 9 with 1% methanol) gave the title compound **112** (176 mg, 44%), as an oil, R_f = 0.28 (ethyl acetate : light petroleum = 1 : 2) (Found: M^+ + H, 534.2747. $C_{34}H_{36}N_3O_3$ requires *M*, 534.2757); ν_{max}/cm^{-1} 3086, 3062, 3029, 2925, 2855, 1747, 1667, 1599, 1550, 1493, 1453, 1405, 1353, 1260, 1154, 1122, 1064, 1026, 983, 913, 821, 741 and 706; δ_H (300 MHz, $CDCl_3$) 1.39–1.55 (2 H, m, cyclobutyl H), 1.61–1.79 (4 H, m, cyclobutyl H), 1.96 (1 H, pent, *J* 9.5 Hz, 6-CH), 2.10 (1 H, d, *J* 12.5 Hz, 5-H), 2.38 (1 H, m, 2-H), 2.47–2.54 (2 H, m, 3-H, 5-H′), 2.64 (1 H, *J* 6.5, 10.5 Hz, 3-H′), 2.83 (1 H, dd, *J* 6.7, 15.2 Hz, 2-CH), 3.04 (1 H, dd, *J* 8.0, 15.2 Hz, 2-CH′), 3.32 and 3.40 (each 1 H, d, *J* 13.0 Hz, PhHC*H*), 3.94 and 4.31 (each 1 H, d, *J* 15.7 Hz, PhHC*H*), 4.32 (1 H, d, *J* 2.5 Hz, 5-H), 6.96 (1 H, s, 4′-H), 7.21–7.27 (10 H, m, ArH), 7.44–7.48 (3 H, m, ArH) and 7.97–8.01 (2 H, m, ArH); δ_C (75 MHz, $CDCl_3$) 17.6, 23.0, 23.4, 26.4, 35.4, 39.3, 44.9, 53.1, 61.9, 64.5, 75.6, 125.4, 126.0, 127.3, 127.4, 127.5, 127.8, 128.3(2), 128.4, 128.7, 128.9, 130.1, 137.8, 138.1, 149.7, 158.8 and 161.2; *m*/*z* (CI^+) 534 (M^+ + 1, 10%) and 108 (100).

(1*RS*,2*RS*,6*SR*)-7-Benzyl-6-cyclobutyl-2-(2-phenyl-1,3-oxazol-5-yl)methyl-4,7-diaza-9-oxabicyclo[4.3.0]nonan-8-one (113). Following the procedure for the preparation of compound **8**, the *N*-benzylpiperidine **112** (170 mg, 0.318 mmol), after stirring for 20 min and chromatography (ethyl acetate with 1% triethylamine to methanol : ethyl acetate = 1 : 10 with 1% triethylamine), gave the title compound **113** (76 mg, 54%), R_f = 0.16 (methanol : ethyl acetate = 1 : 9) (Found: M^+ + H, 444.2285. $C_{27}H_{30}N_3O_3$ requires *M*, 444.2288); ν_{max}/cm^{-1} 3353, 3063, 3031, 2936, 2865, 1744, 1669, 1598, 1550, 1489, 1432, 1408, 1351, 1258, 1164, 1123, 1063, 982 and 913; δ_H (400 MHz,

$CDCl_3$) 1.53–1.96 (6 H, m, 3 × CH_2), 2.28 (1 H, m, 2-H), 2.41 (1 H, d, *J* 14.0 Hz, 5-H), 2.62 (1 H, pent, *J* 8.5 Hz, 6-CH), 2.69 (1 H, d, *J* 14.0 Hz, 5-H′), 2.75 (1 H, t, *J* 12.0 Hz, 3-H), 2.80 (1 H, dd, *J* 6.5, 15.5 Hz, 2-CH), 2.97 (1 H, dd, *J* 5.7, 12.0 Hz, 3-H′), 2.99 (1 H, dd, *J* 8.2, 15.5 Hz, 2-CH′), 4.24 and 4.43 (each 1 H, d, *J* 15.5 Hz, PhHC*H*), 4.51 (1 H, d, *J* 2.2 Hz, 1-H), 6.97 (1 H, s, 4′-H), 7.26–7.39 (5 H, m, ArH), 7.42–7.47 (3 H, m, ArH) and 7.97–8.02 (2 H, m, ArH); δ_C (100 MHz, $CDCl_3$) 17.4, 22.3, 22.9, 26.0, 34.7, 38.6, 43.4, 44.8, 45.0, 63.8, 75.0, 125.4, 126.0, 127.5, 127.8, 128.7(2), 130.1, 138.0, 149.6, 158.5 and 161.2; *m*/*z* (CI^+) 444 (M^+ + 1, 20%) and 206 (100).

(4*SR*,5*RS*)-3-Benzyl-4-(*tert*-butyldimethylsilyloxymethyl)-4-cyclobutyl-5-[3-(3-methoxyphenyl)propen-2-yl]-1,3-oxazolidin-2-one (115). 3-Methoxybenzene boronic acid **114** (4 mg, 0.024 mmol) was added to the bromide **43** (10 mg, 0.02 mmol) in tetrahydrofuran (0.1 mL) and the solution was de-gassed for 10 min. Bis(triphenylphosphine)palladium(II) dichloride (1 mg, 1 μmol) and de-gassed aqueous sodium carbonate (1 M, 0.04 mL, 0.04 μmol) were added and the reaction mixture was heated under reflux for 3 h. Water (5 mL) was added and the mixture was extracted with dichloromethane (3 × 10 mL). The organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue (10% ethyl acetate/light petroleum) gave the title compound **115** (8 mg, 73%) as a colourless oil, R_f 0.47 (20% ethyl acetate/light petroleum) (Found: M^+ + H, 522.3031, $C_{31}H_{44}NO_4Si$ requires *M*, 522.3034); ν_{max}/cm^{-1} 2951, 2930, 2857, 1749, 1599, 1585, 1490, 1464, 1434,1402, 1359, 1259, 1148, 1101, 1051, 837 and 778; δ_H (400 MHz, $CDCl_3$) 0.00 and 0.04 (each 3 H, s, $SiCH_3$), 0.91 [9 H, s, $SiC(CH_3)_3$], 1.54–2.01 (6 H, m, 3 × CH_2), 2.94 (1 H, m, 4-CH), 3.38 (1 H, d, *J* 16.0 Hz, 3′-H), 3.55 (1 H, d, *J* 11.0 Hz, 4-HC*H*), 3.58 (1 H, d, *J* 16.0 Hz, 3′-H′), 3.62 (1 H, d, *J* 11.0, 4-HC*H*), 3.84 (3 H, s, OCH_3), 4.45 and 4.63 (each 1 H, d, *J* 16.0 Hz, PhHC*H*), 4.89 (1 H, s, 5-H), 5.07 and 5.35 (each 1 H, s, 1′-H), 6.84–6.77 (3 H, m, ArH) and 7.25–7.40 (6 H, m, ArH); δ_C (100 MHz, $CDCl_3$) −5.9, −5.7, 17.0, 18.2, 22.8, 23.3, 25.9, 38.2, 39.6, 45.9, 55.2, 63.0, 68.2, 79.0, 112.0, 114.8, 117.1, 121.6, 127.2, 127.5, 128.4, 129.5, 138.7, 139.7, 143.1, 158.9 and 159.8; *m*/*z* (ES^+) 544 (M^+ + 23, 100%).

(4*SR*,5*RS*)-3-Benzyl-4-(*tert*-butyldimethylsilyloxymethyl)-4-cyclobutyl-5-(3-fur-2-ylpropen-2-yl)-1,3-oxazolidin-2-one (117). 2-Furylboronic acid MIDA ester **116** (27 mg, 0.12 mmol) was added to the bromide **43** (30 mg, 0.061 mmol) in tetrahydrofuran (2.5 mL) and the solution was de-gassed for 10 min. Bis(triphenylphosphine)palladium(II) dichloride (3 mg, 4 μmol) and de-gassed aqueous sodium carbonate (2 M, 0.12 mL, 0.24 mmol) were added and the reaction mixture was heated under reflux for 12 h. Water (5 mL) was added and the mixture was extracted with dichloromethane (3 × 10 mL). The organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue (10% ethyl acetate/light petroleum) gave the title compound **117** (21 mg, 72%) as a colourless oil, R_f 0.40 (20% ethyl acetate/light petroleum) (Found: M^+ + H, 482.2710. $C_{28}H_{40}NO_4Si$ requires *M*, 482.2722); ν_{max}/cm^{-1} 2951, 2929, 2857, 1747, 1609, 1510, 1470, 1403, 1359, 1251, 1103, 909, 837, 777 and 731; δ_H (400 MHz, $CDCl_3$) 0.00 and 0.04 (each 3 H, s, $SiCH_3$), 0.90 [9 H, s, $SiC(CH_3)_3$], 1.57–2.03 (6 H, m, 3 × CH_2), 2.93 (1 H, m, 4-CH), 3.50 (1 H, d, *J* 17.0 Hz, 3′-H), 3.55 (1 H, d, *J* 11.0 Hz, 4-*H*CH), 3.57 (1 H, d, *J* 17.0 Hz, 3′-H′), 3.62 (1 H, d, *J* 11.0 Hz, 4-HC*H*), 4.42 and 4.65 (each 1 H, d, *J* 16.0 Hz, Ph*H*CH), 4.96 (1 H, s, 5-H), 5.12 and 5.32 (each 1 H, s, 1′-H), 6.15 and 6.36 (each 1 H, br. d, *J* 3.0 Hz, 3″-H and 4″-H) and 7.27–7.41 (6 H, m, ArH); δ_C (100 MHz, $CDCl_3$) −5.9, −5.8, 17.0, 18.2, 22.8, 23.2, 25.8, 31.7, 38.2, 45.9, 62.9, 68.2, 79.2, 107.4, 110.4, 116.9, 127.2, 127.5, 128.4, 138.6, 140.7, 141.7, 152.0 and 158.9; *m*/*z* (ES^+) 504 (M^+ + 23, 100%).

(4*SR*,5*RS*)-3-Benzyl-4-(*tert*-butyldimethylsilyloxymethyl)-4-cyclobutyl-5-(3-phenylpropen-2-yl)-1,3-oxazolidin-2-one (119). Phenylboronic acid MIDA ester **118** (214 mg, 0.918 mmol) was added to the bromide **43** (227 mg, 0.459 mmol) in tetrahydrofuran (5 mL) and the solution was de-gassed for 10 min. Bis(triphenylphosphine)palladium(II) dichloride (23 mg, 0.032 mmol) and de-gassed aqueous sodium carbonate (2 M, 0.92 mL, 1.84 mmol) were added and the reaction mixture was heated under reflux for 12 h. Water (10 mL) was added and the mixture was extracted with dichloromethane (3 × 10 mL). The organic extracts were dried ($MgSO_4$)and concentrated under reduced pressure. Chromatography of the residue (10% ethyl acetate/light petroleum) gave the title compound **119** (166 mg, 73%) as a colourless oil, R_f 0.60 (20% ethyl acetate/light petroleum) (Found: M^+ + Na, 514.2736. $C_{30}H_{41}NO_3NaSi$ requires *M*, 514.2748); ν_{max}/cm^{-1} 3027, 2949, 2926, 2855, 1744, 1602, 1495, 1453, 1400, 1359, 1291, 1250, 1145, 1098, 1029, 1004, 909, 834, 775 and 732; δ_H (400 MHz, $CDCl_3$) −0.03 and 0.01 (each 3 H, s, $SiCH_3$), 0.87 [9 H, s, $SiC(CH_3)_3$], 1.51–1.96 (6 H, m, 3 × CH_2), 2.92 (1 H, m, 4-CH), 3.37 (1 H, d, *J* 16.0 Hz, 3′-H), 3.54 (1 H, d, *J* 11.0 Hz, 4-*H*CH), 3.58 (1 H, d, *J* 16.0 Hz, 3′-H′), 3.60 (1 H, d, *J* 11.0 Hz, 4-HC*H*), 4.42 and 4.60 (each 1 H, d, *J* 16.0 Hz, Ph*H*CH), 4.86 (1 H, s, 5-H), 5.00 and 5.32 (each 1 H, s, 1′-H) and 7.16–7.37 (10 H, m, ArH); δ_C (100 MHz, $CDCl_3$) −5.9, −5.8, 17.0, 18.1, 22.7, 23.2, 25.8, 38.2, 39.5, 45.9, 63.0, 68.1, 79.0, 117.0, 126.5, 127.2, 127.4, 128.4, 128.5, 129.2, 138.1, 138.6, 143.2 and 158.9; *m*/*z* (ES^+) 514 (M^+ + 23, 100%).

(4*SR*,5*RS*)-3-Benzyl-4-(*tert*-butyldimethylsilyloxymethyl)-4-cyclobutyl-5-[(*RS*)-3-phenyl-1-hydroxyprop-2-yl]-1,3-oxazolidin-2-one (120). Borane (1 M in THF, 2.73 mL, 2.73 mmol) was added dropwise to the alkene **119** (268 mg, 0.545 mmol) in tetrahydrofuran at 0 °C and the mixture was stirred for 16 h at rt. Ethanol (2.5 mL), saturated aqueous NaOAc (8.5 mL) and hydrogen peroxide (30% in water, 3 mL) were added dropwise, and the mixture was heated under reflux for 1.5 h. After cooling to rt, the mixture was extracted with ether, and the organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue (10% ethyl acetate/light petroleum) gave the title compound **120** (166 mg, 73%) as a colourless oil, R_f 0.17 (20% ethyl acetate/light petroleum) (Found: M^+ + Na, 532.2855. $C_{30}H_{43}NO_4NaSi$ requires *M*, 532.2854); ν_{max}/cm^{-1} 3414, 3027, 2927, 2855, 1722, 1603, 1495, 1470, 1453, 1409, 1358, 1293, 1251, 1167, 1100, 1070, 1029, 1003, 980, 835, 775, 745 and 731; δ_H (500 MHz, $CDCl_3$) 0.04 and 0.06 (each 3 H, s, $SiCH_3$), 0.87 [9 H, s, $SiC(CH_3)_3$], 1.46–1.61 (4 H, m, 2 × CH_2), 1.72–1.81 (2 H, m, CH_2), 2.38

(1 H, m, 2′-H), 2.49 (1 H, m, 4-CH), 2.77 and 3.00 (each 1 H, dd, *J* 13.5, 8.0 Hz, 3′-H), 3.67 (2 H, s, 4-CH_2), 3.71 and 3.91 (each 1 H, dd, *J* 11.5, 4.0 Hz, 1′-H), 4.18 (1 H, d, *J* 16.0 Hz, Ph*H*CH), 4.41 (1 H, d, *J* 4.5 Hz, 5-H), 4.62 (1 H, d, *J* 16.0 Hz, PhHC*H*) and 7.21–7.36 (10 H, m, ArH); δ_C (125 MHz, $CDCl_3$) −5.9, −5.7, 17.1, 18.0, 23.0, 23.3, 25.7, 25.8, 36.2, 39.3, 42.1, 45.8, 61.5, 61.7, 68.3, 78.9, 126.5, 127.4, 127.6, 128.5, 128.6, 129.4, 138.4, 139.3 and 159.2; *m*/*z* (ES^+) 532 (M^+ + 23, 100%).

(1*RS*,2*RS*,6*SR*)-7-Benzyl-6-cyclobutyl-2-phenylmethyl-7-aza-4,9-dioxabicyclo[4.3.0]nonan-8-one (122). Triethylamine (5 μL, 0.035 mmol) and mesyl chloride (3 μL, 0.035 mmol) were added to the alcohol **120** (12 mg, 0.024 mmol) in dichloromethane (0.5 mL) at 0 °C and the mixture stirred at rt for 1 h before ether (5 mL) and saturated aqueous NH_4Cl (10 mL) were added. The aqueous phase was extracted with ether (3 × 10 mL) and the organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure to leave mesylate **121** (Found: M^+ + 1, 588.2814. $C_{31}H_{46}NO_6SSi$ requires *M*, 588.2810); *m*/*z* (ES^+) 610 (M^+ + 23, 100%). This was dissolved in tetrahydrofuran (1 mL) and tetrabutylammonium fluoride (1 M in THF, 20 μL, 0.014 mmol) was added at 0 °C. The mixture stirred at rt for 1 h before adding brine (5 mL) then extracted with ethyl acetate (3 × 10 mL). The organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue (25% ethyl acetate/light petroleum) gave the title compound **122** as a colourless oil (5 mg, 56%), R_f 0.26 (20% ethyl acetate/light petroleum) (Found: M^+ + Na, 400.1889. $C_{24}H_{27}NO_3Na$ requires *M*, 400.1884); δ_H (500 MHz, $CDCl_3$) 1.46–1.87 (6 H, m, 3 × CH_2), 2.25 (1 H, m, 2-H), 2.47 (1 H, pent, *J* 7.2 Hz, 6-CH), 2.69 (1 H, dd, *J* 6.5, 13.5 Hz, 2-CH), 2.83 (1 H, dd, *J* 9.0, 13.5 Hz, 2-CH′), 3.27 and 3.49 (each 1 H, d, *J* 12.5 Hz, 5-H), 3.56 (1 H, t, *J* 11.0 Hz, 3-H), 3.79 (1 H, dd, *J* 6.5, 11.0 Hz, 3-H′), 4.29 (1 H, d, *J* 16.0 Hz, Ph*H*CH), 4.33 (1 H, d, *J* 2.5 Hz, 1-H), 4.37 (1 H, d, *J* 16.0 Hz, PhHC*H*) and 7.23–7.35 (10 H, m, ArH); δ_C (125 MHz, $CDCl_3$) 17.8, 22.6, 23.0, 34.2, 37.6, 38.0, 44.9, 63.0, 65.4, 66.1, 74.3, 126.6, 127.7, 127.8, 128.5, 128.6, 128.9, 137.8, 138.2 and 158.5; *m*/*z* (ES^+) 400.5 (M^+ + 23, 100%).

(4*SR*,5*RS*)-3-Benzyl-4-hydroxymethyl-4-cyclobutyl-5-[(*RS*)-3-phenyl-1-hydroxyprop-2-yl]-1,3-oxazolidin-2-one (123). Tetrabutylammonium fluoride (1 M in THF, 0.18 mL, 0.177 mmol) was added to the silyl ether **120** (75 mg, 0.147 mmol) in tetrahydrofuran (1 mL) at 0 °C and the mixture stirred at rt for 1 h. Brine (5 mL) was added and the mixture was extracted with ethyl acetate (3 × 10 mL). The organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue (30% ethyl acetate/light petroleum to neat ethyl acetate) gave the title compound **123** (42 mg, 72%) as a colourless foam, R_f 0.17 (60% ethyl acetate/light petroleum) (Found: M^+ + Na, 418.1989. $C_{24}H_{29}NO_4Na$ requires *M*, 418.1989); ν_{max}/cm^{-1} 3373, 3062, 3026, 2939, 2865, 1713, 1602, 1495, 1412, 1357, 1293, 1252, 1164, 1029, 976, 908 and 729; δ_H (500 MHz, $CDCl_3$) 1.05–1.77 (6 H, m, 3 × CH_2), 2.28 (1 H, pent, *J* 10.0 Hz, 4-CH), 2.46 (1 H, m, 2′-H), 2.60 (2 H, br. s, 2 × OH), 2.67 (1 H, dd, *J* 8.1, 13.5 Hz, 3′-H), 2.91 (1 H, dd, *J* 6.5, 13.5 Hz, 3′-H′), 3.52 and 3.63 (each 1 H, d, *J* 13.0 Hz, 4-*H*CH), 3.80 (1 H, dd, *J* 4.0, 11.0 Hz, 1′-H), 3.89 (1 H, dd, *J* 6.5, 11.0 Hz, 1′-H′), 4.38 (1 H, d, *J* 15.5 Hz, Ph*H*CH), 4.50 (1 H, d, *J* 4.0 Hz, 5-H), 4.52 (1 H, d, *J* 15.5 Hz, PhHC*H*) and 7.20–7.41 (10 H, m, ArH); δ_C (125 MHz, $CDCl_3$) 17.3, 22.5, 22.7, 37.5, 39.2, 42.2, 45.4, 60.4, 62.0, 68.6, 78.4, 126.6, 127.7, 127.9, 128.7, 128.8, 129.4, 138.3, 139.1 and 159.4; *m*/*z* (ES^+) 418.3 (M^+ + 23, 73%) and 396.3 (M^+ + 1, 35).

(1*RS*,2*RS*,6*SR*)-4,7-Bis-benzyl-6-cyclobutyl-2-phenylmethyl-4,7-diaza-9-oxabicyclo[4.3.0]nonan-8-one (125). Mesyl chloride (0.03 mL, 0.364 mmol) and triethylamine (0.06 mL, 0.455 mmol) were added to the diol **123** (36 mg, 0.091 mmol) in dichloromethane (1.7 mL) at 0 °C and the mixture was warmed to room temperature and stirred for 1 h. Saturated aqueous NH_4Cl (5 mL) was added and the aqueous layer was extracted with ether (3 × 10 mL). The organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure to give the bis-mesylate **124**. This bis-mesylate was dissolved in benzylamine (3 mL) and the solution stirred at 90 °C for 18 h. After cooling to room temperature, the solution was concentrated under reduced pressure and chromatography of the residue (5% to 10% ethyl acetate/light petroleum) gave the title compound **125** (27 mg, 64%) as an oil, R_f 0.4 (33% ethyl acetate/light petroleum) (Found: M^+ + H, 467.2700. $C_{31}H_{35}N_2O_2$ requires *M*, 467.2694); ν_{max}/cm^{-1} 3029, 2940, 1742, 1592, 1491, 1451, 1429, 1405, 1343, 1169, 1053 and 743; δ_H (500 MHz, $CDCl_3$) 1.20–1.70 (5 H, m, cyclobutyl-H), 1.88 (1 H, pent, *J* 9.5 Hz, cyclobutyl-H), 2.10 (1 H, d, *J* 11.0 Hz, 5-H), 2.20 (1 H, m, 2-H), 2.46 (2 H, m, 6-CH, 5-H′), 2.58 (2 H, m, 3-H_2), 2.75 (1 H, dd, *J* 7.0, 13.0 Hz, 2-*H*CH), 2.88 (1 H, dd, *J* 9.0, 13.0 Hz, 2-HC*H*), 3.35 and 3.41 (each 1 H, d, *J* 13.0 Hz, Ph*H*CH), 3.89 (1 H, d, *J* 16.0 Hz, Ph*H*CH), 4.18 (1 H, d, *J* 2.0 Hz, 1-H), 4.32 (1 H, d, *J* 16.0 Hz, PhHC*H*) and 7.25–7.37 (15 H, m, ArH); δ_C (125 MHz, $CDCl_3$) 17.5, 23.1, 23.8, 36.3, 38.3, 39.3, 44.8, 52.6, 53.7, 61.9, 64.5, 75.5, 126.3, 127.2, 127.3, 127.8, 128.2, 128.3, 128.5, 128.9, 129.0, 138.0, 138.3, 138.9 and 159.2; *m*/*z* (ES^+) 467 (M^+ + 1, 100%).

Studies of the biological activity of the 2-(2-furyl)oxazolidinonylpiperidine 64. M_1 receptor-mediated functional responses were measured as the relaxation responses of spontaneously contracting rat duodenum.[29] Isolated segments of rat duodenum were set up in Tyrodes solution gassed with O_2 95% and CO_2 5% and maintained at 37 °C and isometric tension was recorded under a resting tension of 1.5 g using a PowerLab/4SP computer system (AD Instruments, Charlgrove, Oxfordshire, UK). Concentration-response curves were constructed by adding either the selective M_1 receptor agonist McN-A-343 or the piperidine **64** to the bath non-cumulatively in increasing half logarithmic concentrations. Each dose was left in the bath for 1 min or until a maximum effect was produced before washout. To examine the effect of piperidine **64** on responses to McN-A-343, a concentration-response curve for McN-A-343 was obtained first and in the same tissue repeated in the presence of piperidine **64** (10^{-7} M) added to the bath 15 min before each dose of McN-A-343. Piperidine **64** (10^{-7} M) did not affect the resting rhythmic activity of the rat duodenum, indicating that there was no direct agonist (orthosteric) activity at M_1 receptors. However, in its presence the concen-

tration-response curve for the relaxation by McN-A-343 (EC_{50} 0.48(0.20–0.38)μM) was significantly shifted 10.6 ± 7.7-fold to the left compared with in the absence of piperidine **64** (1.16 (0.42–7.36)μM). This indicates potentiation of the responses. By contrast, the vehicle for piperidine **64**, DMSO, had no effect on the dose–response curves for the M_1 receptor agonist. The same concentration of piperidine **64** (10^{-7} M) had a small inhibitory effect on the concentration-response curve for methacholine contractions on the guinea-pig ileum. However, this shift to the right was not significant. The 2-furyloxazolidinonylpiperidine **64** therefore appears to be a positive allosteric modulator of the muscarinic M_1 receptor as it potentiates the effects of an M_1 receptor agonist without causing agonist or antagonistic activity on its own. There was minimal activity at M_3 receptors of the guinea-pig ileum as the contractions to methacholine were not significantly affected.

X-Ray data

Epoxide **29**: $C_{17}H_{31}NO_4Si$; unit cell parameters: *a* 12.1292(18) *b* 14.039(2) *c* 12.6549(19); *P*21/*c*, CCDC number 1413287.

Alcohol **41**: $C_{25}H_{30}N_2O_3$; unit cell parameters: *a* 22.546(14) *b* 9.314(10) *c* 10.283(9); *P*21/*c*, CCDC number 1413286.

Diol **46**: $C_{26}H_{33}NO_5$; unit cell parameters: *a* 10.4841(7) *b* 13.2138(9) *c* 33.919(2); *P*21/*c*, CCDC number 1413288.

Amine **84**: $C_{24}H_{28}N_2O_3$; unit cell parameters: *a* 11.874(3) *b* 18.239(4) *c* 9.829(2) beta = 94.881(4); *P*21/*c*; *R*(int) = 0.0726, $R_1[I > 2\sigma(I)] = 0.0534$. CCDC 1424601.

Piperidine **106**: $C_{30}H_{30}N_3O_7S$; *a* 13.818(2) *b* 14.714(2) *c* 14.863(3) alpha = 76.010(4) beta = 82.840(4), gamma = 70.291(3); *P*$\bar{1}$; *R*(int) = 0.1125, $R_1[I > [2\sigma(I)] = 0.0668$. CCDC 1424602.

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