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A synthesis of a common intermediate to the lactone–pyrrolidinone ring systems in oxazolomycin A and neooxazolomycin

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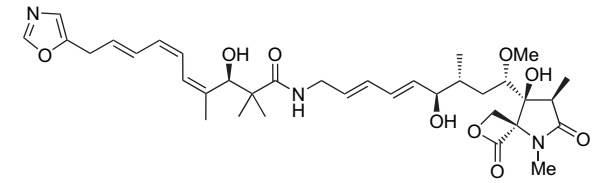
Abstract—A 5-*exo*-dig radical cyclisation of the bromoamide **34** derived from the enantiopure α-ethynyl substituted amino alcohol **31** led to a 2:1 mixture of β-C3 and α-C3 methyl epimers of the pyrrolidinone **35a–36a** in a combined yield of 73%. Treatment of the homoallylic alcohol **35b**, derived from **35a**, with OsO_4–TMEDA, gave a single diastereoisomer of the pyrrolidinone triol **37**, resulting from selective dihydroxylation from the β-face, i.e. *syn* to the CH_2OH group of **35b**. The pyrrolidinone triol **37** is a potential common precursor, cf. **9**, to the spiro β-lactone pyrrolidinone **8** and the γ-lactone pyrrolidinone **10** ring systems in oxazolomycin A (**1**) and neooxazolomycin **2**, respectively. Sequential protection of the 1,2-diol functionality in **37** as the acetonide **39**, and the primary alcohol group in **39** as the SEM ether **41a**, followed by methylation of the nitrogen centre in **41a**, using NaH–MeI, then gave the selectively protected pyrrolidinone **42**.

1. Introduction

Oxazolomycin A (**1**) and neooxazolomycin **2** are the parent compounds of a family of novel lactone/pyrrolidinone-based metabolites, which were first isolated in 1985 by Uemera et al.,[1] from the fermentation broth of *Streptomyces* sp. Both compounds display potent antibiotic properties and strong anticancer activity,[2] in addition to antiviral activity against vaccinia, herpes simplex type I and influenza.[3] Oxazolomycin A has also been found to inhibit crown gall formation in plants caused by *Agrobacterium tumefacieus*.[2,4]

Several *Z*/*E* geometrical isomers about the conjugated triene unit in oxazolomycin A (**1**), designated oxazolomycins B, C and D, were later isolated from *S. albus*.[5] In addition, the 16-methyloxazolomycins **3a**,[6] together with the 'curromycins' **3b** and **3c**,[7] which contain an additional methyl group at C-2 in their oxazole rings, have also been isolated from *Streptomyces* sp. More recently, the unusual nitro-tetraene antibiotic substance lajollamycin **4**, which contains the same spiro-β-lactone-γ-lactam structural features common to the oxazolomycins, has been isolated from the marine actinomycete *S. nodosus*.[8,9]



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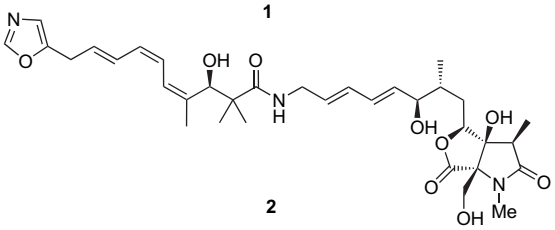

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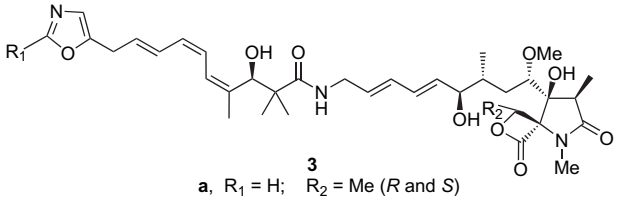
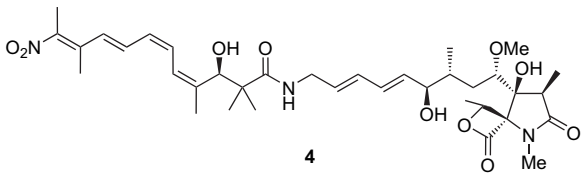


3

a, R_1 = H; R_2 = Me (*R* and *S*)
b, R_1 = Me; R_2 = CH_3OCH_2
c, R_1 = Me; R_2 = Me



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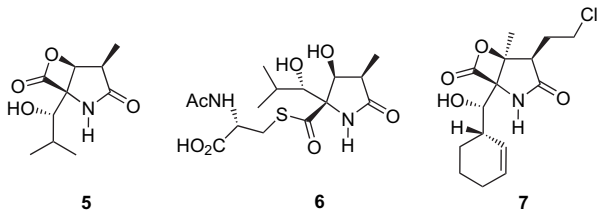
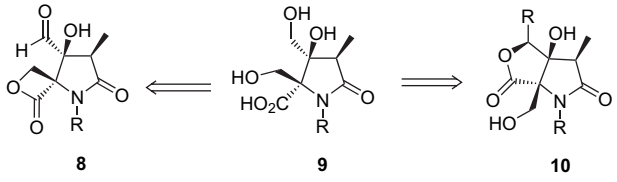
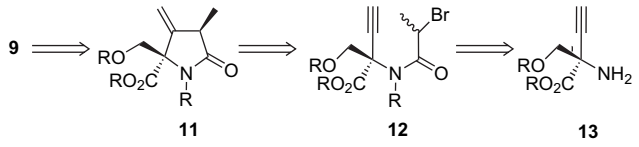


The oxazolomycins **1**–**3**, with their lactone ring-fused pyrrolidinone motifs, show an uncanny structural relationship to the 20S proteasome inhibitors omuralide **5**[10] (cf. lactacystin **6**)[11] and salinosporamide A **7**,[12] which are showing potential in therapy for the treatment of various cancers, also Alzeimer's disease and asthma.[13] Although there has been substantial synthetic work directed towards lactacystin **6**, omuralide **5** and salinsporamide **7**,[14] a total synthesis of oxazolomycin A (**1**) and its relatives **3** and **4** has yet to be achieved. However, several years ago Kende et al.[15] described a total synthesis of neooxazolomycin **2**, and a number of research groups have developed and/or studied routes to the polyene segments and to the β-lactone/pyrrolidinone ring system in the oxazolomycins **1** and **3a**.[16] In this paper we describe our studies of the synthesis of the triol-substituted pyrrolidinone **9**, which we plan to use as a common precursor to both the β-lactone and γ-lactone pyrrolidinone ring systems, **8** and **10**, respectively, found in oxazolomycin A (**1**) and neooxazolomycin **2**.



2. Results and discussion

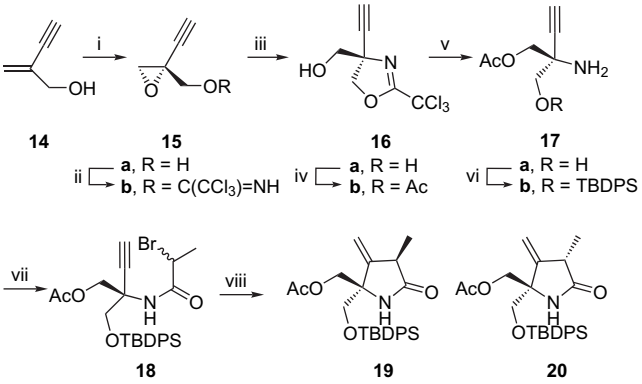
Our synthetic approach to the triol-substituted pyrrolidinone **9** was based on elaboration of the enantiopure 4-methylenepyrrolidinone **11**, followed by diastereoselective dihydroxylation. In turn, and in parallel with contemporaneous synthetic work towards lactacystin **6**,[17a] we planned to synthesise the 4-methylenepyrrolidinone **11**, by way of a 5-*exo*-dig radical cyclisation of the acetylenic bromoamide **12**[17b] derived from the enantiopure amine **13** (Scheme 1).[18,19]



Scheme 1. Retrosynthesis of **9** from **13**.

α,α-Disubstituted α-amino acid units are found in a number of natural products and methods for their synthesis have been the subject of a recent review.[20] We evaluated a number of these methods[17c] en route to the α-ethynyl amino acid derivative **13**, including the ring opening of chiral aziridines,[21] and the use of Seebach's 'self-regeneration of stereocentre' protocol from chiral oxazolidines.[22] Ultimately, we found that the method of Schmidt and Hatakeyama,[23] involving the synthesis and ring opening of enantiopure 3,3-disubstituted 2-trichloromethyl oxazolines was particularly suitable for the synthesis of the α-ethynyl serine derivative **13**.[17a,c]

Thus, a Sharpless epoxidation of the known enynol **14**,[24] under optimum conditions,[25] using (−)-diisopropyl tartrate, titanium tetraisopropoxide and cumene hydroperoxide at −12 °C for 15 h first gave the (*S*)-(+)-epoxide **15a** in 77% yield, with an ee of 83%, as determined by a Mosher's ester analysis. When the same epoxidation was carried out at lower temperatures, i.e. −20 °C or −40 °C, the yields and the ee were considerably poorer. Treatment of the epoxide **15a** with trichloroacetonitrile in the presence of DBU at 0 °C next gave the corresponding acetimidate **15b**, which was then cyclised to the oxazoline **16a** using $AlEt_2Cl$. In our first investigations, we next protected the alcohol group in **16a** as its acetate **16b**. Treatment of the oxazoline **16b**, with dilute hydrochloric acid then gave the amino alcohol **17a**, which was not isolated, but instead it was immediately reacted with TBDPSCl leading to the crystalline silyl-ether derivative **17b** (Scheme 2).



Scheme 2. Reagents and conditions: (i) 20% $Ti(O^iPr)_4$, 26% D-(−)-DIPT, cumene hydroperoxide, CH_2Cl_2, −12 °C, 15 h, 77%, 83% ee; (ii) CCl_3CN, DBU, CH_2Cl_2, 0 °C, 1 h, 81%; (iii) $AlEt_2Cl$, CH_2Cl_2, 0 °C to rt, 15 h, 63%; (iv) AcCl, DMAP, Et_3N, CH_2Cl_2, 0 °C, 1.5 h, 94%; (v) 1 M HCl, THF, rt, 3 h; (vi) TBDPSCl, DMAP, Et_3N, CH_2Cl_2, rt, 5 h, 76% over two steps; (vii) 2-bromopropionoyl chloride, Et_3N, CH_2Cl_2, rt, 15 h, 50%; (viii) Bu_3SnH, AIBN, toluene, reflux, 2 h, 55%, 3:4 mixture of diastereoisomers.

Treatment of the α-ethynyl amine **17b** with 2-bromopropionoyl chloride gave a 1:1 mixture of diastereoisomers of the amide **18** in 50% yield.[17a] When a solution of the acetylenic bromoamide **18** in refluxing toluene was treated dropwise, via a syringe pump, with a solution of Bu_3SnH in toluene containing catalytic AIBN, followed by heating under reflux for 2 h, work-up and chromatography gave the anticipated 4-methylenepyrrolidinone **19** but as a 4:3 mixture of C-3 methyl epimers, in 55% yield. The epimers **19** and **20** could be separated by chromatography and NOE studies showed that the major diastereoisomer, unfortunately, had the unwanted α-methyl stereochemistry at C-3, i.e. **20**. The relevant NOE data are collected on the structures in Figure 1. The poor selectivity during the 5-*exo*-dig radical cyclisation of **18** was disappointing but perhaps not too surprising. We had hoped that the larger TBDPS protecting group on the hydroxymethyl group at the quaternary centre in **18** would favour cyclisation to the diastereoisomer **19** where the C-3 methyl and C-5 $CH_2OTBDPS$ groups would have an *anti*-relationship.

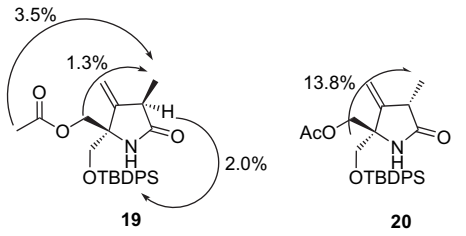
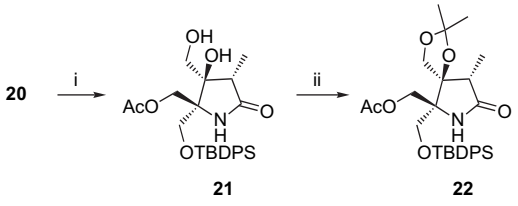


Figure 1. ^{1}H NOE enhancement data for the epimeric 4-methylenepyrrolidinones **19** and **20**.

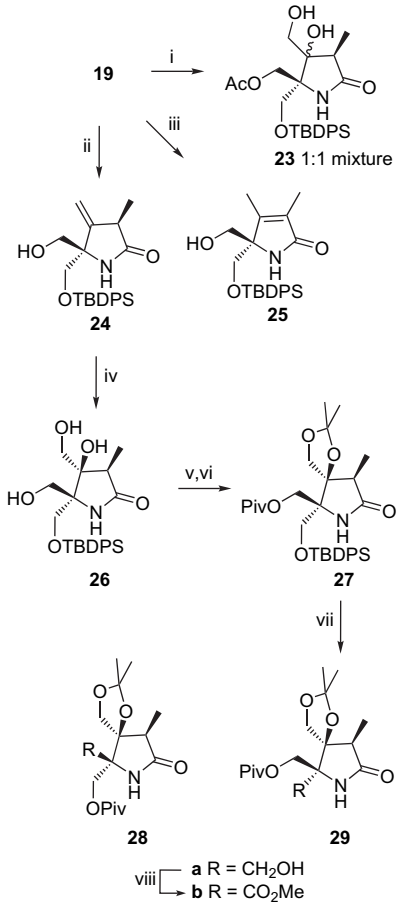
Unperturbed, at this point the C-3 α- and β-methyl epimers, **20** and **19**, were separately dihydroxylated using catalytic OsO_4 and NMO in acetone–water.[26] Anticipating that the C-3 methyl and C-5 $CH_2OTBDPS$ groups in the epimer **20** would operate in concert to promote dihydroxylation from the β-face of the 4-methylene group,[27] we were not surprised to observe the formation of a single diastereoisomeric vicinal diol, i.e. **21**, from dihydroxylation of **20**. The stereochemistry of **21** followed from NOE studies on the corresponding acetonide derivative **22** produced by treatment of **21** with 2,2-dimethoxypropane in the presence of *p*TSA (Scheme 3). It was all the more disappointing then to find that when we treated the corresponding C-3 β-methyl epimer **19** with OsO_4 and NMO, under the same reaction conditions, a 1:1 mixture of C-4 hydroxy epimers of the vicinal diol **23** was obtained. Clearly, in **19** the β-orientated C-3 methyl group exercises a steric effect to render the β-face of the C-4 methylene group equally unfavourable to vicinal dihydroxylation from this face of the molecule, and hence no selectivity ensued.



Scheme 3. Reagents and conditions: (i) OsO_4, NMO, acetone/H_2O (1:1), rt, 4 days, 59%; (ii) 2,2-dimethoxypropane, *p*TSA, rt, 15 h, 88%.

In contemporaneous studies Donohoe et al.[28] had extolled the virtues of directed dihydroxylation of allylic and homoallylic alcohols using OsO_4 in the presence of TMEDA at −78 °C. We were attracted to this procedure for the conversion of the homoallylic alcohol **24**, derived from the acetate **19**, into the diastereoisomer **26** of the corresponding triol, which had most of the functionality and, more importantly, the stereochemical detail in our target pyrrolidinone triol **9**. Thus, after optimisation of the reaction conditions, the acetate **19** was hydrolysed to the corresponding alcohol **24** in 89% yield using 5 equiv of titanium isopropoxide in isopropanol at room temperature for 3 h.[29] A significant by-product, using alternative methods, e.g., $NaBH_4$,[30] $LiBH_4$, $NaBH_3CN$, BF_3OEt_2,[31] $(Bu_3Sn)_2O$,[32] was the positional isomer **25** of the desired product **24**; indeed when **19** was treated with K_2CO_3 in methanol at room temperature for 15 h, the isomer **25** of **24** was obtained in 80% yield (Scheme 4). Nevertheless, we were delighted to find that when the homoallylic alcohol **24** was treated with OsO_4–TMEDA only one diastereoisomer of the resulting triol **26** was produced. The stereochemistry of **26** followed from studies, in association with HMBC and ROESY experiments, of the ^{1}H and ^{13}C NMR spectra of the corresponding acetonide–pivalate ester **27**, which was produced from **26**, in two straightforward steps. Furthermore, the relative stereochemistry of **27** was confirmed by observing a number of key enhancements in the ROESY experiments.

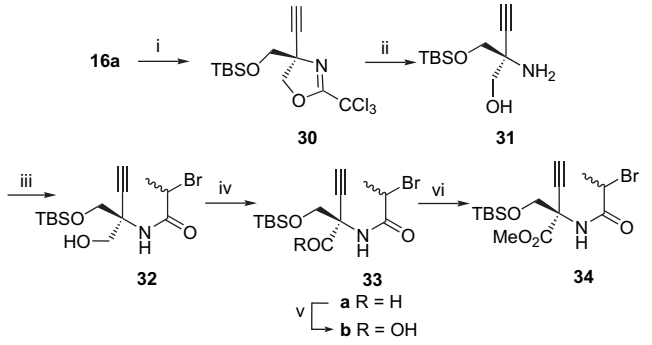
We were now in a position to convert the $CH_2OTBDPS$ group in **27** into the corresponding carboxylic acid ester, and thereby complete a synthesis of a fully protected derivative, viz. **29b**, of the target pyrrolidinone triol **9**. It was to our disappointment therefore that when the silyl ether **27** was treated with TBAF in THF at room temperature for 1.5 h, work-up gave a mixture of the isomeric alcohols **28a** and **29a**, resulting from deprotection and in situ partial migration, i.e. transesterification, of the adjacent pivalate group (Scheme 3). Furthermore, the diastereoisomeric alcohol **28a** with the 'wrong' stereochemistry for subsequent elaboration to **9** was the major product resulting from the deprotection, i.e. 3:1, **28a**–**29a**. Nevertheless, this mixture of alcohols was treated with RuO_2–$NaIO_4$, followed by trimethylsilyldiazomethane, to give a mixture of the



Scheme 4. Reagents and conditions: (i) OsO_4, NMO, acetone/H_2O (1:1), rt, 4 days, 47%; (ii) $Ti(O^iPr)_4$, IPA, rt, 3 h, 89%; (iii) K_2CO_3, MeOH, rt, 15 h, 80%; (iv) OsO_4, TMEDA, CH_2Cl_2, −78 °C, 1 h, 35%; (v) 2,2-dimethoxypropane, *p*TSA, rt, 3 h, 48%; (vi) trimethylacetyl chloride, pyridine, DMAP, 40 °C, 24 h, 67%; (vii) TBAF, THF, rt, 1.5 h, 64%; (viii) $NaIO_4$, $RuO_2 \cdot H_2O$, CH_3CN, CCl_4, rt, 5 h, then TMS–CHN_2, 1 h, 91%.

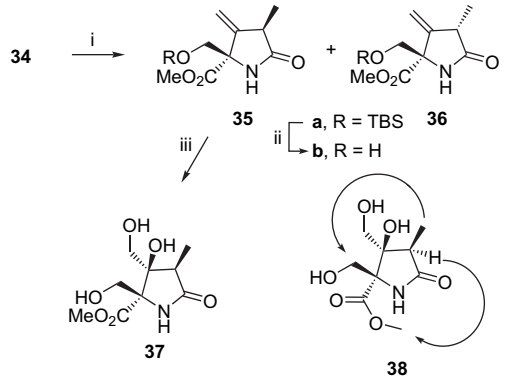
corresponding methyl esters **28b** and **29b**, respectively, from which the major diastereoisomer **28b** could be separated and characterised.

We decided at this juncture to throw caution to the wind and examine a more direct approach to the synthesis of the triol **9** using a radical cyclisation of the bromoamide **34**, which already had an ester function at the quaternary centre. The hydroxyl group in the previously synthesised oxazoline **16a** was therefore first protected as its TBS ether **30**. The protected oxazoline **30** was next treated with dilute hydrochloric acid to reveal the α-ethynyl amine **31**, which was immediately converted into the corresponding amide **32** following treatment with 2-bromopropionoyl chloride (Scheme 5). The primary alcohol group in **32** was now oxidised, in sequence, to the aldehyde **33a** and to the carboxylic acid **33b**, which was then esterified using trimethylsilyldiazomethane leading to the corresponding methyl ester **34**[33] (Scheme 5).



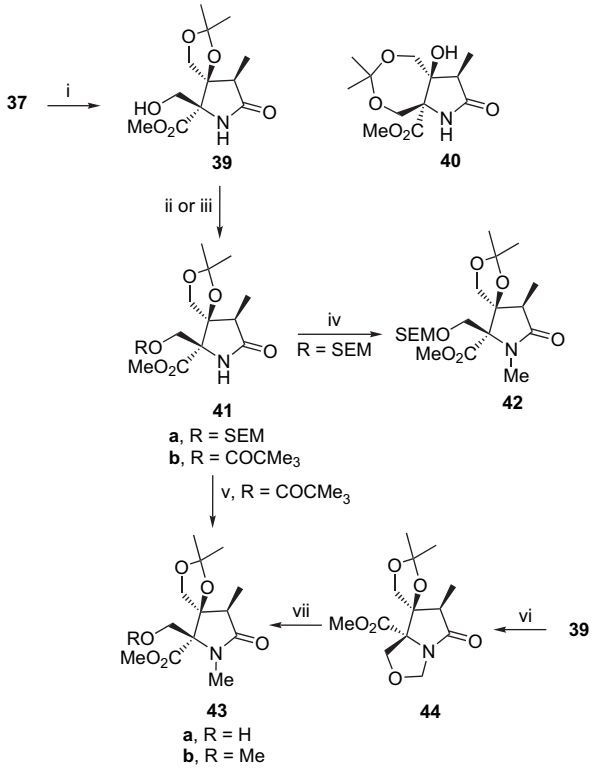
Scheme 5. Reagents and conditions: (i) TBSCl, imidazole, CH_2Cl_2, rt, 15 h, 83%; (ii) 1 M HCl, THF, rt, 3 h; (iii) 2-bromopropionoyl chloride, $NaHCO_3$, CH_2Cl_2, rt, 2 h, 76% (for two steps); (iv) TPAP, NMO, CH_2Cl_2, rt, 2 h, 88%; (v) $NaClO_2$, NaH_2PO_4, ^tBuOH, 2-methyl-2-butene, rt, 6 h, 83%; (vi) TMS–CHN_2, MeOH/benzene (1:2.5), rt, 1 h, 75%.

Significantly, when a solution of the bromoamide **34** in refluxing toluene was treated with Bu_3SnH–AIBN, under the same conditions as those used with the substrate **18**, a much more stereoselective 5-*exo*-dig cyclisation ensued leading to a 2:1 mixture of β- and α-C-3 epimers, i.e. **35a** and **36a**, of the anticipated methylenepyrrolidinone, and in a combined yield of 73%. The epimers **35a** and **36a** were not separated at this stage but, instead, the mixture was treated with *p*TSA in THF/H_2O, which gave a 2:1 mixture of the corresponding homoallylic alcohols **35b** and **36b** in a combined yield of 65%, which could be separated by chromatography (Scheme 6). The stereochemistries of the pyrrolidinones **35b** and **36b** were then confirmed by selective NOE enhancements in their ^1H NMR spectra, and comparison of these data with those of similar intermediates we had synthesised in our contemporaneous studies towards lactacystin **6**.[17a] To our pleasure, when the 4-methylenepyrrolidinone **35b** was treated with OsO_4–TMEDA in CH_2Cl_2 at −78 °C for 1 h and then at room temperature for 2 h, a selective dihydroxylation occurred from the β-face, i.e. *syn* to the CH_2OH group, leading to a single diastereoisomer of the pyrrolidinone triol **37**, which was obtained in an excellent 99% yield.[34] The stereochemistry of the triol **37** followed from NOE enhancements in the ^1H NMR spectrum, and the pertinent enhancements are collected on structure **38**. The pyrrolidinone triol **37** has the same stereochemistry at the three contiguous asymmetric centres as those in the pyrrolidinone core **9** of oxazolomycin A (**1**) and neooxazolomycin **2**.



Scheme 6. Reagents and conditions: (i) Bu_3SnH, AIBN, toluene, reflux, 2 h, 73%, 2:1 mixture of diastereoisomers; (ii) *p*TSA, THF/H_2O, rt, 15 h, **35b** 39% and **36b** 26%, 2:1 mixture of diastereoisomers; (iii) OsO_4, TMEDA, CH_2Cl_2, −78 °C to rt, 3 h, 99%.

In anticipation of using the pyrrolidinone triol **37** as a common intermediate to both oxazolomycin A (**1**) and neooxazolomycin **2**, we prepared a number of its derivatives including the acetonide **39**, the SEM acetonide **41** and the *N*-methyl derivatives **42** and **43**. Thus, treatment of the triol **37** with 2,2-dimethoxypropane in CH_2Cl_2 in the presence of



Scheme 7. Reagents and conditions: (i) 2,2-dimethoxypropane, *p*TSA, CH_2Cl_2, 15 h, rt, 39%; (ii) trimethylacetyl chloride, Et_3N, DMAP, CH_2Cl_2, 40 °C, 24 h, 67%; (iii) [2-(trimethylsilyl)ethoxy]methyl chloride, TBAI, Et_3N, rt, 15 h, 23%; (iv) NaH, DMF, 0 °C 10 min then MeI, 0 °C, 1 h, 100%; (v) NaH, DMF, 0 °C,10 min then MeI, 0 °C, 1 h, 60% (**43b**); (vi) $(CHO)_n$, $MgSO_4$, toluene, 110 °C, 8 h, 57%; (vii) Et_3SiH, TFA, CH_2Cl_2, 0 °C to rt, 15 h, 23% (**43a**).

catalytic *p*TSA at room temperature for 15 h gave the expected acetonide **39**, albeit in a modest 39% yield (Scheme 6). Interestingly, when the same reaction was terminated after 3 h, the only product isolated was the isomeric seven-membered ring ketal **40**.[35] We presume that **40** is the kinetic product of the protection of the triol **37**, which rearranges to the thermodynamic product **39** with additional time. The primary alcohol group in the acetonide **39** could then be protected as the SEM ether **41a** and as the pivalate **41b**. However, although the SEM ether **41a** could be methylated on nitrogen in quantitative yield using NaH–MeI, leading to the *N*-methyl pyrrolidinone **42**, similar treatment of the pivalate ester **41b** with NaH–MeI resulted in methyl ether–pivalate exchange in addition to methylation on nitrogen leading to **43b** in 60% yield. Finally, reaction of the substituted pyrrolidinone **39** with paraformaldehyde in the presence of $MgSO_4$ and *p*TSA[36] gave the corresponding ring-fused oxazolidine **44** in 57% yield, which could be cleaved with Et_3SiH–TFA to the *N*-methyl pyrrolidinone **43a** (Scheme 7).

3. Summary and conclusion

In summary, we have developed a useful synthetic approach to the pyrrolidinone triol **37** and its derivatives **39**, **41a**, **41b**, **42**, **43a**, **43b** and **44**, which we plan to use as common precursors to the lactone–pyrrolidinone ring systems, viz. **8** and **10**, in oxazolomycin A (**1**) and neooxazolomycin **2**, and hence to the natural products themselves. The syntheses of the pyrrolidinone triol derivatives are based on a diastereoselective 5-*exo*-dig radical cyclisation of a bromoamide, i.e. **34**, derived from an enantiopure α-ethynyl substituted amino alcohol, i.e. **31**, followed by a stereoselective vicinal dihydroxylation of a 5-hydroxymethyl substituted 4-methylenepyrrolidinone intermediate, viz. **35b**, using OsO_4–TMEDA, as key steps.

4. Experimental

4.1. General details

Proton NMR spectra were recorded on a Bruker DRX 360 (360.13 MHz), a Bruker AV 400 (400.13 MHz), or a Bruker DRX 500 (500.12 MHz) spectrometer, at ambient temperature, as dilute solutions in deuterated chloroform. Data are expressed as chemical shifts in parts per million (ppm) relative to the residual protonated solvent used as an internal standard (δ_H=7.27 ppm for $CDCl_3$). The multiplicity of a signal is designated by one of the following abbreviations: s, singlet; d, doublet; t, triplet, q, quartet; br, broad and m, multiplet. All coupling constants, *J*, are quoted in hertz (Hz). ^{13}C NMR spectra were recorded on a Bruker DRX 360 (90.03 MHz), a Bruker AV 400 (100.03 MHz), or a Bruker DRX 500 (125 MHz) spectrometer, at ambient temperature, as dilute solutions in deuterated chloroform. Data are expressed as chemical shifts in parts per million (ppm) relative to the residual solvent used as an internal standard (δ_C=77.0 ppm for the central peak of $CDCl_3$). Assignments of ^{13}C spectra were made on the basis of chemical shift using a DEPT sequence with secondary pulses at 90° and 135°, where appropriate. H–H COSY, HMQC, HMBC and NOE experiments were recorded on a Bruker AM400 (400.13 MHz) and were used to confirm ^1H and ^{13}C assignments, as appropriate.

IR spectra were recorded as dilute solutions in spectroscopic grade chloroform on a Perkin Elmer FTIR 1600 instrument. Optical rotations were recorded on a JASCO DIP 370 polarimeter.

Mass spectra were recorded on a VG Autospec MM-701CF or Micromass LCT spectrometer using electro-ionisation (EI), chemical ionisation (CI), fast atom bombardment (FAB) or electrospray (ES) techniques. High-resolution mass spectra were calculated from the molecular formula corresponding to the observed signal, using the most abundant isotopes of each element, to four decimal places.

Melting points (mps) were determined on a Bibby Stuart Scientific SMP3 apparatus and are uncorrected.

Flash column chromatography was carried out on Merck silica gel 60 as the stationary phase, and the solvents used for elution were of analytical grade. All reactions were monitored by thin layer chromatography using silica gel 60 F_{254} precoated aluminium backed plates, which were viewed under UV light and then developed in basic potassium permanganate or phosphomolybdic acid.

Unless stated otherwise, reactions requiring anhydrous conditions were conducted under an inert atmosphere of nitrogen or argon in flame dried apparatus. Experiments were generally performed using distilled organic solvents. Diethyl ether and tetrahydrofuran were distilled from sodium metal and benzophenone ketal under a nitrogen atmosphere. Toluene was distilled from sodium wire and dichloromethane from calcium hydride. Anhydrous *N*,*N*-dimethylformamide was purchased from Aldrich. Evaporations of organic solutions were carried out using a Buchi rotary evaporator under reduced pressure.

4.1.1. (*S*)-2-Oxiranyl-but-3-yn-1-ol (15a). Titanium tetraisopropoxide (1.14 mL, 3.66 mmol) and diisopropyl-D-tartrate (1.00 mL, 4.76 mmol) were added in one portion to a stirred suspension of powdered 3 Å molecular sieves (1.5 g) in dichloromethane (60 mL) at −12 °C. The mixture was stirred at −12 °C for 30 min and then the enynol **14** (1.5 g, 18.3 mmol)[24] was added in a single portion followed by cumene hydroperoxide (10.1 mL, 54.9 mmol) in a single portion. The mixture was stirred at −12 °C for 15 h and then diluted with a solution of citric acid (1.5 g) in diethyl ether/acetone (9:1; 150 mL). The resulting suspension was filtered through a pad of Celite and the filtrate was then concentrated in vacuo. The residue was purified by flash column chromatography, on silica gel, eluting with pentane/diethyl ether (1:1) to give the epoxide (1.40 g, 77%) as a colourless oil; $[\alpha]_D^{24}$ 48.4 (*c* 1.0, $CHCl_3$); ν_{max} ($CHCl_3$) 3590, 3304, 2926, 2880 cm^{-1}; δ_H (360 MHz, $CDCl_3$) 3.91 (1H, d, *J*=12.7, CH_2OH), 3.76 (1H, d, *J*=12.7, CH_2OH), 3.07 (1H, d, *J*=5.5, CH_2OC), 3.03 (1H, d, *J*=5.5, CH_2OC), 2.40 (1H, s, C≡C*H*); δ_C (90 MHz, $CDCl_3$) 79.9 (*C*≡CH), 73.3 (C≡*C*H), 62.9 (*C*H_2OH), 51.2 (*C*H_2OC), 50.7 (quat. C).

4.1.2. (*S*),(*S*)-Mosher ester of the epoxide (15a). *S*-(−)-Methoxytrifluoromethylphenylacetic acid (18 μL,

0.098 mmol) was added to a stirred solution of the epoxide **15** (8 mg, 0.082 mmol), triethylamine (23 μL, 0.16 mmol) and *N*,*N*-dimethylaminopyridine (1 mg) in deuterated chloroform (0.5 mL) at room temperature. The solution was stirred at room temperature for 2 h and then diluted with a saturated aqueous solution of sodium bicarbonate (0.5 mL). The organic phase was separated and the aqueous phase was extracted with dichloromethane (2×1 mL). The organic extracts were combined, dried over $MgSO_4$ and evaporated in vacuo. The residue was purified by flash column chromatography, on silica gel, eluting with pentane/diethyl ether (1:1) to give the (*S*)-ester (5 mg, 32%) as a colourless oil and as an 11:1 mixture of diastereoisomers (corresponding to an enantiomeric excess of 83%) that was not separated; Major diastereoisomer: $[\alpha]_D^{24}$ −12.5 (*c* 0.8, $CHCl_3$); ν_{max} ($CHCl_3$) 3304, 2958, 1756 cm^{-1}; δ_H (360 MHz, $CDCl_3$) 7.59–7.57 (2H, m, Ar-*H*), 7.47–7.41 (3H, m, Ar-*H*), 4.66 (1H, d, *J*=12.0, CH_2OCO), 4.41 (1H, d, *J*=12.0, CH_2OCO), 3.62 (3H, s, OCH_3), 3.08 (1H, d, *J*=5.4, CH_2OC), 2.90 (1H, d, *J*=5.4, CH_2OC), 2.37 (1H, s, C≡C*H*); δ_C (90 MHz, $CDCl_3$) 166.0 (*C*=O), 131.8 (Ar-*C*), 129.7 (Ar-*C*H), 128.4 (Ar-*C*H), 127.7 (Ar-*C*H), 124.7 (*C*CF_3), 121.5 (*C*F_3), 78.7 (*C*≡CH), 73.4 (C≡*C*H), 66.1 (*C*H_2OCO), 55.6 (O*C*H_3), 52.1 (*C*H_2OC), 47.8 (quat. *C*); δ_F (282 MHz) −72.23; *m*/*z* found 315.0857, 337.0649, 378.0931 (M+H^+, $C_{15}H_{14}O_4F_3$ requires 315.0844; M+Na, $C_{15}H_{13}O_4F_3Na$ requires 337.0664; M+Na+CH_3CN, $C_{17}H_{16}O_4F_3NaN$ requires 378.0929).

4.1.3. (*R*),(*S*)-Mosher ester of the epoxide (15a). The Mosher ester was prepared from the epoxide **15** and *R*-(+)-methoxytrifluoromethylphenylacetic acid using the same procedure as that described for the diastereoisomer. Flash column chromatography gave the (*R*)-ester (5 mg, 32%) as a colourless oil and as an 11:1 mixture of diastereoisomers (corresponding to an enantiomeric excess of 83%) that was not separated; Major diastereoisomer: $[\alpha]_D^{24}$ +21.0 (*c*, 0.8, $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 3304, 2953, 1756; δ_H (360 MHz, $CDCl_3$) 7.57–7.54 (2H, m, Ar-*H*), 7.45–7.38 (3H, m, Ar-*H*), 4.72 (1H, d, *J*=12.1, CH_2OCO), 4.33 (1H, d, *J*=12.1, CH_2OCO), 3.60 (3H, s, OCH_3), 3.06 (1H, d, *J*=5.4, CH_2OC), 2.95 (1H, d, *J*=5.4, CH_2OC), 2.41 (1H, s, C≡C*H*); δ_C (90 MHz, $CDCl_3$) 166.0 (*C*=O), 131.8 (Ar-*C*), 129.7 (Ar-*C*H), 128.4 (Ar-*C*H), 127.4 (Ar-*C*H), 124.7 (*C*CF_3), 121.5 (*C*F_3), 78.8 (*C*≡CH), 73.4 (C≡*C*H), 65.8 (*C*H_2OCO), 55.6 (O*C*H_3), 52.0 (*C*H_2OC), 48.4 (quat. *C*); δ_F (282 MHz) −72.15; *m*/*z* found 315.0825, 337.0639, 378.0917 (M+H^+, $C_{15}H_{14}O_4F_3$ requires 315.0844; M+Na, $C_{15}H_{13}O_4F_3Na$ requires 337.0664; M+Na+CH_3CN, $C_{17}H_{16}O_4F_3NaN$ requires 378.0929).

4.1.4. 2,2,2-Trichloroacetimidic acid (*S*)-2-ethynyl-oxiranylmethyl ester (15b). Trichloroacetonitrile (3.14 mL, 31.3 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (0.47 mL, 3.1 mmol) were added in a single portion to a stirred solution of the epoxide **15a** (2.56 g, 26.1 mmol) in dichloromethane (100 mL) at 0 °C. The mixture was stirred at 0 °C for 1 h and then diluted with water (50 mL). The organic phase was separated and the aqueous phase was extracted with dichloromethane (3×30 mL). The combined organic extracts were dried over $MgSO_4$ and evaporated in vacuo. The residue was purified immediately by flash column chromatography through a short pad of silica gel, eluting with pentane/diethyl ether (3:2) to give the trichloroacetimidate (5.1 g, 81%) as a yellow oil; $[\alpha]_D^{24}$ 19.6 (*c* 1.0, $CHCl_3$); ν_{max} ($CHCl_3$) 3305, 2958, 1669 cm^{-1}; δ_H (360 MHz, $CDCl_3$) 8.46 (1H, br s, N*H*), 4.60 (1H, d, *J*=12.0, CH_2O), 4.45 (1H, d, *J*=12.0, CH_2O), 3.13 (1H, d, *J*=5.6, CH_2OC), 3.11 (1H, d, *J*=5.6, CH_2OC), 2.41 (1H, s, C≡C*H*); δ_C (90 MHz, $CDCl_3$) 162.2 (*C*=NH), 79.1 (*C*≡CH), 77.2 (*C*Cl_3), 73.1 (C≡*C*H), 68.8 (*C*H_2O), 52.1 (*C*H_2OC), 48.2 (quat. *C*); *m*/*z* (CI, NH_4^+) found 241.9544 (M+H^+, $C_7H_7O_2NCl_3$ requires 241.9542).

4.1.5. [(*R*)-2-Trichloromethyl-4-ethynyl-4,5-dihydro-oxazole]methanol (16a). A solution of diethylaluminium chloride (1 M in hexanes; 10.3 mL, 10.3 mmol) was added over 5 min to a stirred solution of the acetimidate **15b** (5.0 g, 20.7 mmol) in dichloromethane (100 mL) at 0 °C. The mixture was stirred at 0 °C for 1 h and then allowed to warm to room temperature over 15 h before being quenched with a saturated aqueous solution of sodium bicarbonate (50 mL). The organic phase was separated and the aqueous phase was then extracted with dichloromethane (3×30 mL). The combined organic extracts were dried over $MgSO_4$ and evaporated in vacuo. The residue was purified by flash column chromatography, on silica gel, eluting with pentane/ether (1:1) to give the oxazoline (3.14 g, 63%) as a colourless oil; $[\alpha]_D^{24}$ −18.4 (*c* 1.0, $CHCl_3$); ν_{max} ($CHCl_3$) 3595, 3305, 2937, 1655 cm^{-1}; δ_H (360 MHz, $CDCl_3$) 4.82 (1H, d, *J*=8.4, CH_2O), 4.70 (1H, d, *J*=8.4, CH_2O), 3.96 (1H, d, *J*=11.7, CH_2OH), 3.72 (1H, d, *J*=11.7, CH_2OH), 2.62 (1H, s, C≡C*H*), 2.25 (1H, br s, O*H*); δ_C (90 MHz, $CDCl_3$) 165.2 (*C*=N), 80.9 (*C*≡CH), 77.8 (*C*H_2O), 77.2 (*C*Cl_3), 75.6 (C≡*C*H), 69.9 (quat. *C*), 66.7 (*C*H_2OH); *m*/*z* (ES) 241.9553 (M+H^+, $C_7H_7O_2NCl_3$ requires 241.9542).

4.1.6. (*S*),(*R*)-Mosher ester of the alcohol (16a). *S*-(−)-Methoxytrifluoromethylphenylacetic acid (9 μL, 0.045 mmol) was added to a stirred solution of the oxazoline **16a** (10 mg, 0.041 mmol), triethylamine (9 μL, 0.06 mmol) and *N*,*N*-dimethylaminopyridine (1 mg) in deuterated chloroform (0.5 mL) at room temperature. The solution was stirred at room temperature for 2 h and then diluted with a saturated aqueous solution of sodium bicarbonate (0.5 mL). The organic phase was separated and the aqueous phase was extracted with dichloromethane (2×1 mL). The combined organic extracts were dried over $MgSO_4$ and evaporated in vacuo. The residue was purified by flash column chromatography, on silica gel, eluting with pentane/diethyl ether (1:1) to give the (*S*)-ester (11 mg, 64%) as a colourless oil and as an 11:1 mixture of diastereoisomers (corresponding to an enantiomeric excess of 83%) that was not separated; Major diastereoisomer: $[\alpha]_D^{24}$ −12.8 (*c* 0.5, $CHCl_3$); ν_{max} ($CHCl_3$) 3305, 2953, 1759, 1657 cm^{-1}; δ_H (360 MHz, $CDCl_3$) 7.51–7.50 (2H, m, Ar-*H*), 7.43–7.41 (3H, m, Ar-*H*), 4.70 (1H, d, *J*=8.8, CH_2O), 4.66 (1H, d, *J*=8.8, CH_2O), 4.56 (1H, d, *J*=11.3, CH_2O), 4.53 (1H, d, *J*=11.3, CH_2O), 3.55 (3H, s, OCH_3), 2.66 (1H, s, C≡C*H*); δ_C (90 MHz, $CDCl_3$) 165.9 (*C*=O), 165.2 (*C*=N), 131.5 (Ar-*C*), 129.9 (2× Ar-*C*H), 128.6 (Ar-*C*H), 128.5 (Ar-*C*H), 127.4 (Ar-*C*H), 124.7 (*C*CF_3), 121.5 (*C*F_3), 79.8 (*C*≡CH), 77.9 (*C*H_2O), 77.2 (*C*Cl_3), 76.2 (C≡*C*H), 68.1 (*C*H_2O), 67.3 (quat. *C*), 55.5 (O*C*H_3); δ_F (282 MHz) −72.12; *m*/*z* found 457.9937, 459.9955 (M+H^+, $C_{17}H_{14}O_4NF_3{}^{35}Cl_3$ requires 457.9941; M+H^+, $C_{17}H_{14}O_4NF_3{}^{35}Cl_2{}^{37}Cl$ requires 459.9911).

4.1.7. (*R*),(*R*)-Mosher ester of the alcohol (16a). The Mosher ester was prepared from the alcohol **16a** and *R*-(+)-methoxytrifluoromethylphenylacetic acid using the same procedure as that described for the diastereoisomer. Flash column chromatography, on silica gel, eluting with pentane/diethyl ether (1:1) gave the (*S*)-ester (10 mg, 53%) as a colourless oil and as an 11:1 mixture of diastereoisomers (corresponding to an enantiomeric excess of 83%) that was not separated; Major diastereoisomer: $[\alpha]_D^{24}$ 19.0 (*c* 0.2, $CHCl_3$); ν_{max} ($CHCl_3$) 3305, 1007 cm^{-1}; δ_H (360 MHz, $CDCl_3$) 7.50–7.48 (2H, m, Ar-*H*), 7.43–7.41 (3H, m, Ar-*H*), 4.68 (1H, d, *J*=8.8, CH_2O), 4.61 (1H, d, *J*=11.4, CH_2O), 4.53 (1H, d, *J*=8.8, CH_2O), 4.49 (1H, d, *J*=11.4, CH_2O), 3.54 (3H, s, OCH_3), 2.66 (1H, s, C≡C*H*); δ_C (90 MHz, $CDCl_3$) 165.9 (*C*=O), 165.2 (*C*=N), 131.5 (Ar-*C*), 129.9 (Ar-*C*H), 129.6 (Ar-*C*H), 128.6 (2×Ar-*C*H), 127.4 (Ar-*C*H), 124.7 (*C*CF_3), 121.5 (*C*F_3), 79.6 (*C*≡CH), 77.8 (*C*H_2O), 77.2 (*C*Cl_3), 76.4 (C≡*C*H), 68.1 (*C*H_2O), 67.6 (quat. *C*), 55.5 (O*C*H_3); δ_F (282 MHz) −71.99; *m/z* found 457.9978 (M+H^+, $C_{17}H_{14}O_4NF_3{}^{35}Cl_3$ requires 457.9941).

4.1.8. [(*R*)-4-Ethynyl-2-(trichloromethyl)-4,5-dihydro-1,3-oxazol-4-yl]methyl acetate (16b). Acetyl chloride (0.88 mL, 12.4 mmol) was added over 5 min to a stirred solution of the oxazoline **16a** (2.0 g, 8.3 mmol), triethylamine (2.3 mL, 16.6 mmol) and *N*,*N*-dimethylaminopyridine (0.1 g, 0.83 mmol) in anhydrous dichloromethane (30 mL) at 0 °C. The solution was stirred at 0 °C for 1.5 h and then diluted with water (30 mL). The organic phase was separated and the aqueous phase was then extracted with dichloromethane (3×30 mL). The combined organic extracts were dried over $MgSO_4$ and then evaporated in vacuo. The residue was purified by flash column chromatography, on silica gel, eluting with pentane/ether (1:1) to give the acetate (2.2 g, 94%) as a yellow oil; $[\alpha]_D^{24}$ −6.0 (*c* 1.0, $CHCl_3$); Found: C, 38.0; H, 3.1; N, 4.6; $C_9H_8O_3NCl_3$ requires C, 38.2; H, 2.9; N, 5.0%; ν_{max} ($CHCl_3$) 3305, 2959, 2130, 1731, 1651 cm^{-1}; δ_H (360 MHz, $CDCl_3$) 4.73 (1H, d, *J*=8.7, CH_2O), 4.68 (1H, d, *J*=8.7, CH_2O), 4.37 (1H, d, *J*=11.4, CH_2O), 4.31 (1H, d, *J*=11.4, CH_2O), 2.65 (1H, s, C≡C*H*), 2.09 (3H, s, COCH_3); δ_C (90 MHz, $CDCl_3$) 170.1 (*C*OCH_3), 164.7 (*C*=N), 85.9 (CCl_3), 79.9 (*C*≡CH), 78.0 (CH_2O), 75.9 (C≡*C*H), 67.9 (quat. *C*), 66.9 (*C*H_2OH), 20.6 (CO*C*H_3); *m/z* (ES) found 283.9629 (M+H^+ $C_9H_9O_3NCl_3$ requires 283.9648).

4.1.9. Acetic acid (*R*)-2-amino-2-(*tert*-butyl-diphenyl-silanyloxymethyl)-but-3-ynyl ester (17b). Aqueous hydrochloric acid (1 M, 3.9 mL, 3.9 mmol) was added in a single portion to a stirred solution of the oxazoline **16b** (1.1 g, 3.9 mmol) in tetrahydrofuran (22 mL) at room temperature. The solution was stirred at room temperature for 3 h and then the solvent was evaporated in vacuo to leave the amino alcohol **17a**. The alcohol was dissolved immediately in dichloromethane (15 mL) and triethylamine (3 mL), and then *tert*-butyldiphenylsilyl chloride (3.1 mL, 11.7 mmol) and *N*,*N*-dimethylaminopyridine (50 mg, 0.39 mmol) were added in one portion. The mixture was stirred at room temperature for 5 h, and then diluted with a saturated aqueous solution of sodium bicarbonate (10 mL) and dichloromethane (10 mL). The organic phase was separated and the aqueous phase was then extracted with dichloromethane (2×10 mL) and ethyl acetate (3×10 mL). The combined organic extracts were dried over $MgSO_4$ and evaporated in vacuo. The residue was purified by flash column chromatography, on silica gel, eluting with dichloromethane/methanol (4:1) to give a yellow solid, which was recrystallised from pentane/ethyl acetate (20:1) to give the amine (1.2 g, 76%) as a pale yellow solid; mp 67–68 °C; $[\alpha]_D^{24}$ −3.2 (*c* 1.0, $CHCl_3$); ν_{max} ($CHCl_3$) 3429, 3306, 2932, 2859 cm^{-1}; δ_H (360 MHz, $CDCl_3$) 7.70–7.67 (4H, m, Ar-*H*), 7.47–7.38 (6H, m, Ar-*H*), 4.21 (1H, d, *J*=10.7, CH_2O), 4.16 (1H, d, *J*=10.7, CH_2O), 3.72 (1H, d, *J*=9.6, CH_2O), 3.68 (1H, d, *J*=9.6, CH_2O), 2.32 (1H, s, C≡C*H*), 2.08 (3H, s, COCH_3), 1.73 (2H, br s, NH_2), 1.08 (9H, s, SiC(CH_3)$_3$); δ_C (90 MHz, $CDCl_3$) 170.4 (*C*OCH_3), 135.6 (2×Ar-*C*H), 135.5 (2×Ar-*C*H), 132.5 (Ar-*C*), 132.4 (Ar-*C*), 130.1 (4×Ar-*C*H), 127.9 (Ar-*C*H), 127.8 (Ar-*C*H), 81.2 (*C*≡CH), 73.4 (C≡*C*H), 66.6 (*C*H_2O), 66.3 (*C*H_2O), 57.6 (quat. *C*), 26.8 (SiC*Me*$_3$), 23.8 (CO*C*H_3), 19.3 (Si*C*Me$_3$); *m/z* (ES+) found 418.1814 (M+Na, $C_{23}H_{29}O_3NSiNa$ requires 418.1814).

4.1.10. (2*R*)-2-[(2-Bromopropanoyl)amino]-2-({[(1,1-dimethylethyl)(diphenyl)silyl]oxy}methyl)-3-butyn-1-yl acetate (18). 2-Bromopropionyl chloride (0.6 mL, 5.85 mmol) was added dropwise, over 5 min, to a stirred solution of the amine **17b** in dichloromethane (15 mL) and triethylamine (0.5 mL) at room temperature. The mixture was stirred at room temperature for 15 h and then diluted with a saturated aqueous solution of potassium carbonate (5 mL), water (5 mL) and dichloromethane (10 mL). The organic phase was separated and the aqueous phase was then extracted with dichloromethane (3×10 mL). The combined organic extracts were dried over $MgSO_4$ and evaporated in vacuo. The residue was purified by flash column chromatography, on silica gel, eluting with pentane/ether (polarity increasing from 7:3 to 1:1) to give a 1:1 mixture of diastereoisomers of the amide (1.01 g, 50% for three steps) as a pale yellow oil; $[\alpha]_D^{24}$ −1.6 (*c* 3.0, $CHCl_3$); ν_{max} ($CHCl_3$) 3397, 3306, 2932, 2860, 1746 cm^{-1}; δ_H (360 MHz, $CDCl_3$) 7.74–7.67 (8H, m, Ar-*H*×2), 7.43–7.39 (12H, m, Ar-*H*×2), 7.05 (2H, s, N*H*), 4.60–4.57 (2H, m, CH_2O), 4.40–4.36 (4H, m, CH_2O), 4.01–3.87 (4H, m, CH_2O and C*H*Br), 2.41 (2H, s, C*H*≡C×2), 2.02 (6H, s, CH_3CO), 1.90–1.87 (6H, m, CH_3C×2), 1.11–1.06 (18H, s, Si*C*(*C*H_3)$_3$); δ_C (90 MHz, $CDCl_3$) 170.3 (*C*OCH_3), 168.7 (*C*ONH), 168.4 (*C*ONH), 135.5 (8×Ar-*C*H), 132.2 (4×Ar-*C*), 130.0 (4×Ar-*C*H), 129.8 (4×Ar-*C*H), 127.8 (2×Ar-*C*H), 127.7 (2×Ar-*C*H), 79.6 (2×*C*≡CH), 73.5 (2×C≡*C*H), 64.9 (2×*C*H_2O), 63.3 (*C*H_2O), 63.1 (*C*H_2O), 54.8 (quat. *C*), 54.5 (quat. *C*), 45.0 (*C*HBrCH$_3$), 44.7 (*C*HBrCH$_3$), 26.7 (2×SiC*Me*$_3$), 22.8 (Si*C*Me$_3$), 22.4 (Si*C*Me$_3$), 20.6 (*C*OCH_3), 19.2 (*C*OCH_3); *m/z* (ES) found 530.1347, 552.1217, 554.1197 (M+H^+, $C_{26}H_{33}O_4NSi^{79}Br$ requires 530.1362; M+Na, $C_{26}H_{32}O_4NSi^{79}BrNa$ requires 552.1182; M+Na, $C_{26}H_{32}O_4NSi^{81}BrNa$ requires 554.1161).

4.1.11. [(2*R*,4*R*)-2-({[(1,1-Dimethylethyl)(diphenyl)-silyl]oxy}methyl)-4-methyl-3-methylidene-5-oxo-2-pyrrolidinyl]methyl acetate (19) and [(2*R*,4*S*)-2-({[(1,1-dimethylethyl)(diphenyl)silyl]oxy}methyl)-4-methyl-3-methylidene-5-oxo-2-pyrrolidinyl]methyl acetate (20). A solution of tributyltin hydride (0.20 mL, 0.75 mmol) and 2,2′-azobisisobutyronitrile (20 mg, 0.12 mmol) in degassed toluene (30 mL) was added dropwise over 0.5 h, via syringe

pump, to a refluxing solution of the amide **18** (0.33 g, 0.62 mmol) in degassed toluene (125 mL) under an atmosphere of argon. The solution was heated under reflux for a further 2 h, then cooled to room temperature and evaporated in vacuo. The residue was partitioned between acetonitrile (50 mL) and hexane (50 mL). The acetonitrile extract was separated and the hexane phase extracted with acetonitrile (30 mL). The combined acetonitrile extracts were evaporated in vacuo and the residue was purified by flash column chromatography, on silica gel, eluting with pentane/diethyl ether (7:3) then diethyl ether to give (i) the β-methyl pyrrolidinone **19** (eluted first) (0.21 g, 27%) as a colourless oil; $[\alpha]_D^{24}$ 0.85 (*c* 0.7, $CHCl_3$); ν_{max} ($CHCl_3$) 3427, 2932, 2859, 1708 cm^{-1}; δ_H (360 MHz, $CDCl_3$) 7.68–7.60 (4H, m, Ar-*H*), 7.48–7.37 (6H, m, Ar-*H*), 5.73 (1H, s, N*H*), 5.14 (1H, s, C=CH_2), 5.13 (1H, s, C=CH_2), 4.45 (1H, d, *J*=11.3, CH_2O), 4.03 (1H, d, *J*=11.3, CH_2O), 3.64 (1H, d, *J*=10.2, CH_2O), 3.62 (1H, d, *J*=10.2, CH_2O), 3.07–3.03 (1H, m, C*H*CH_3), 2.02 (3H, s, COCH_3), 1.33 (3H, d, *J*=7.4, CHCH_3), 1.06 (9H, s, SiC(CH_3)$_3$); δ_C (90 MHz, $CDCl_3$) 177.3 (*C*ONH), 170.5 (*C*OCH$_3$), 148.4 (*C*=CH$_2$), 135.6 (2×Ar-*C*H), 135.5 (2×Ar-*C*H), 132.4 (2×Ar-*C*), 130.0 (4×Ar-*C*H), 127.9 (2×Ar-*C*H), 109.7 (C=*C*H$_2$), 67.0 (CH_2O), 66.3 (CH_2O), 64.8 (quat. *C*), 40.8 (*C*HCH$_3$), 26.8 (SiC*Me*$_3$), 20.7 (Si*C*Me$_3$), 19.2 (CO*C*H$_3$), 16.0 (CH*C*H$_3$); *m*/*z* (ES) found 452.2255, 515.2352 (M+H$^+$, $C_{26}H_{34}O_4NSi$ requires 452.2257; M+Na$^+$+CH_3CN $C_{28}H_{36}O_4N_2SiNa$ requires 515.2342); In a ^{1}H NOE experiment (400 MHz, $CDCl_3$), irradiation at δ 4.45 gave an enhancement at δ 1.33 (1.3%); irradiation at δ 4.03 gave an enhancement at δ 1.33 (1.3%); irradiation at δ 3.05 gave an enhancement at δ 1.06 (2%); irradiation at δ 2.02 gave an enhancement at δ 1.33 (3.5%) and irradiation at δ 1.33 gave an enhancement at δ 2.02 (1.6%); and (ii) the α-methyl pyrrolidinone **20** (eluted second) (0.22 g, 28%); $[\alpha]_D^{24}$ −3.7 (*c* 0.6, $CHCl_3$); ν_{max} ($CHCl_3$) 3428, 2959, 2932, 2860, 1743, 1709, 1664, 1375, 1113 cm^{-1}; δ_H (360 MHz, $CDCl_3$) 7.65–7.61 (4H, m, Ar-*H*), 7.46–7.41 (6H, m, Ar-*H*), 5.92 (1H, s, N*H*), 5.09 (1H, s, C=CH_2), 5.08 (1H, s, C=CH_2), 4.43 (1H, d, *J*=11.0, CH_2O), 4.07 (1H, d, *J*=11.0, CH_2O), 3.73 (1H, d, *J*=10.2, CH_2O), 3.57 (1H, d, *J*=10.2, CH_2O), 3.12–3.08 (1H, m, C*H*CH_3), 2.02 (3H, s, CH_3CO), 1.27 (3H, d, *J*=7.4, CH_3CH), 1.09 (9H, s, SiC(CH_3)$_3$); δ_C (90 MHz, $CDCl_3$) 177.3 (*C*ONH), 170.5 (*C*OCH$_3$), 148.5 (*C*=CH$_2$), 135.6 (2×Ar-*C*H), 135.6 (2×Ar-*C*H), 132.4 (2×Ar-*C*), 130.1 (4×Ar-*C*H), 127.9 (Ar-*C*H), 127.9 (Ar-*C*H), 109.5 (C=*C*H$_2$), 66.3 (2×CH_2O), 64.4 (quat. *C*), 41.0 (*C*HCH$_3$), 26.8 (SiC*Me*$_3$), 20.8 (CO*C*H$_3$), 19.2 (Si*C*Me$_3$), 15.7 (CH*C*H$_3$); *m*/*z* found 474.2115 (M+Na, $C_{26}H_{33}O_4NSiNa$ requires 474.2077). In a ^{1}H NOE experiment (400 MHz, $CDCl_3$), irradiation at δ 3.73 gave an enhancement at δ 1.27 (13.8%) and irradiation at δ 3.57 gave an enhancement at δ 1.27 (3.9%).

4.1.12. [(2*R*,3*S*,4*S*)-2-({[(1,1-Dimethylethyl)(diphenyl)-silyl]oxy}methyl)-3-hydroxy-3-(hydroxymethyl)-4-methyl-5-oxo-2-pyrrolidinyl]methyl acetate (21). A solution of osmium tetroxide (4% in water; 0.26 mL) was added to a stirred solution of the pyrrolidinone **20** (0.18 g, 0.4 mmol) and *N*-methylmorpholine-*N*-oxide (61 mg, 0.6 mmol) in acetone/water (1:1; 2.5 mL) at room temperature. The suspension was stirred at room temperature for 4 days, and then a saturated aqueous solution of sodium sulfite (5 mL) was added and the solution was stirred for a further 1 h. The suspension was diluted with ethyl acetate (5 mL) and the organic phase was then separated. The aqueous phase was extracted with ethyl acetate (3×5 mL) and then with isopropanol/chloroform (1:1; 10 mL). The combined organic extracts were evaporated in vacuo and the residue was purified by flash column chromatography, on silica gel, eluting with ethyl acetate to give the vicinal diol (0.23 g, 59%) as a colourless oil; $[\alpha]_D^{24}$ 3.0 (*c* 0.1, $CHCl_3$); ν_{max} ($CHCl_3$) 3694, 2961, 1712, 1602, 1097 cm^{-1}; δ_H (360 MHz, $CDCl_3$) 7.65–7.62 (4H, m, Ar-*H*), 7.45–7.39 (6H, m, Ar-*H*), 5.85 (1H, s, N*H*), 4.43–4.35 (2H, m, CH_2O), 3.95–3.60 (4H, m, CH_2O×2), 2.65 (1H, q, *J*=7.7, CH_3C*H*), 1.92 (3H, s, CH_3CO), 1.13–1.04 (12H, m, SiC(CH_3)$_3$ and CH_3CH); δ_C (90 MHz, $CDCl_3$) 176.8 (*C*OCH$_3$), 170.7 (*C*ONH), 135.6 (2×Ar-*C*H), 135.2 (2×Ar-*C*H), 134.8 (2×Ar-*C*), 131.8 (Ar-*C*H), 131.6 (Ar-*C*H), 130.3 (Ar-*C*H), 129.6 (Ar-*C*H), 128.0 (Ar-*C*H), 127.7 (Ar-*C*H), 79.8 (*C*OH), 78.3 (quat. *C*), 65.6 (*C*H$_2$OH), 63.3 (*C*H$_2$O), 62.7 (*C*H$_2$O), 46.6 (*C*HCH$_3$), 26.8 (SiC*Me*$_3$), 20.8 (CO*C*H$_3$), 19.1 (Si*C*Me$_3$), 10.7 (CH*C*H$_3$); *m*/*z* (EI) found 486.2320, 549.2366 (M+H$^+$, $C_{26}H_{36}O_6NSi$ requires 486.2312, M+CH_3CN+Na$^+$, $C_{28}H_{38}O_6N_2SiNa$ requires 549.2397).

4.1.13. [(5*S*,6*R*,9*S*)-6-({[(1,1-Dimethylethyl)(diphenyl)-silyl]oxy}methyl)-2,2,9-trimethyl-8-oxo-1,3-dioxa-7-azaspiro[4.4]non-6-yl]methyl acetate (22). *para*-Toluenesulfonic acid (2 mg) was added to a stirred solution of the diol **21** (0.23 g, 0.47 mmol) in 2,2-dimethoxypropane (2 mL) and the mixture was stirred at room temperature for 15 h. The mixture was diluted with a saturated aqueous solution of sodium bicarbonate (2 mL) and ethyl acetate (2 mL). The organic phase was separated and the aqueous phase was then extracted with ethyl acetate (3×2 mL). The combined organic extracts were dried over $MgSO_4$ and then evaporated in vacuo to leave the acetonide (0.22 g, 88%) as a colourless oil, which was used without further purification; $[\alpha]_D^{24}$ 1.5 (*c* 0.2, $CHCl_3$); ν_{max} ($CHCl_3$) 2929, 2857, 1708, 1114 cm^{-1}; δ_H (360 MHz, $CDCl_3$) 7.65–7.60 (4H, m, Ar-*H*), 7.47–7.39 (6H, m, Ar-*H*), 5.71 (1H, s, N*H*), 4.39 (1H, d, *J*=11.4, CH_2O), 4.26 (1H, d, *J*=11.4, CH_2O), 4.11 (1H, d, *J*=9.9, CH_2O), 3.96 (1H, d, *J*=9.9, CH_2O), 3.67 (2H, s, CH_2O), 2.81 (1H, q, *J*=7.7, C*H*CH$_3$), 1.96 (3H, s, CH_3CO), 1.38 (3H, s, CH_3C), 1.30 (3H, s, CH_3C), 1.17 (3H, d, *J*=7.7, CHCH_3), 1.08 (9H, s, SiC(CH_3)$_3$); δ_C (90 MHz, $CDCl_3$) 176.1 (*C*OCH$_3$), 170.2 (*C*ONH), 135.6 (2×Ar-*C*H), 135.5 (2×Ar-*C*H), 132.0 (2×Ar-*C*), 130.2 (Ar-*C*H), 130.1 (Ar-*C*H), 129.5 (Ar-*C*H), 128.0 (Ar-*C*H), 127.9 (Ar-*C*H), 127.6 (Ar-*C*H), 109.3 (*C*Me$_2$), 87.2 (*C*(O)), 64.9 (*C*H$_2$O), 64.1 (quat. *C*), 63.6 (*C*H$_2$O), 63.2 (*C*H$_2$O), 45.5 (*C*HCH$_3$), 26.8 (SiC*Me*$_3$), 26.0 (CCH_3×2), 20.8 (CO*C*H$_3$), 19.1 (Si*C*Me$_3$), 11.0 (CH*C*H$_3$); *m*/*z* (ES) found 526.2646 (M+H$^+$, $C_{29}H_{40}O_6NSi$ requires 526.2625). In a ^{1}H NOE experiment (400 MHz, $CDCl_3$), irradiation at δ 4.11 gave enhancements at δ 3.67 (12.7%) and 1.17 (0.7%); irradiation at δ 3.96 gave enhancements at δ 3.67 (2.2%) and 1.17 (3.6%); irradiation at δ 3.67 gave enhancements at δ 4.11 (11.5%), 3.96 (14.1%) and 1.17 (2.6%); irradiation at δ 2.81 gave enhancements at δ 4.26 (1.9%) and 1.38 (2.3%); irradiation at δ 1.38 gave an enhancement at δ 2.81 (2.5%) and irradiation at δ 1.17 gave an enhancement at δ 3.96 (3.5%).

4.1.14. [(2*R*,4*R*)-2-({[(1,1-Dimethylethyl)(diphenyl)-silyl]oxy}methyl)-3-hydroxy-3-(hydroxymethyl)-4-methyl-5-oxo-2-pyrrolidinyl]methyl acetate (23). A solution of osmium tetroxide (4% in water; 0.1 mL) was added to a stirred solution of the pyrrolidinone **19** (70 mg, 0.16 mmol) and *N*-methylmorpholine-*N*-oxide (24 mg, 0.23 mmol) in acetone/water (1:1; 2.5 mL). The suspension was stirred at room temperature for 6 days, and then diluted with a saturated aqueous solution of sodium sulfite (2 mL). The solution was stirred for a further 1 h and then diluted with ethyl acetate (2 mL). The organic phase was separated and the aqueous phase was extracted with ethyl acetate (3×2 mL) and isopropanol/chloroform (1:1; 5 mL). The combined organic extracts were evaporated in vacuo and the residue was purified by flash column chromatography, on silica gel, eluting with ethyl acetate to give a 1:1 mixture of diastereoisomers of the vicinal diol (37 mg, 47%) as a colourless oil; $[\alpha]_D^{24}$ −3.0 (*c* 0.2, $CHCl_3$); ν_{max} ($CHCl_3$) 2961, 1711, 1601, 1092 cm^{-1}; δ_H (360 MHz, $CDCl_3$) 7.67–7.61 (8H, m, Ar-*H*), 7.48–7.41 (12H, m, Ar-*H*), 5.96 (1H, s, N*H*), 5.88 (1H, s, N*H*), 4.47–4.22 (4H, m, CH_2O×2), 3.94–3.60 (8H, m, CH_2O×4), 2.81–2.67 (1H, m, $CHCH_3$), 2.53–2.50 (1H, m, $CHCH_3$), 2.04 (3H, s, CH_3CO), 1.93 (3H, s, CH_3CO), 1.29–1.05 (24H, m, $SiC(CH_3)_3$×2, $CHCH_3$×2); δ_C (90 MHz, $CDCl_3$) 177.0 ($COCH_3$), 176.9 ($COCH_3$), 170.8 ($CONH$×2), 135.7 (Ar-*C*H), 135.6 (Ar-*C*H), 135.6 (4×Ar-*C*H), 135.5 (4×Ar-*C*H), 131.9 (2×Ar-*C*), 131.8 (2×Ar-*C*), 130.3 (8×Ar-*C*H), 128.0 (4×Ar-*C*H), 80.3 (*C*(OH)), 75.1 (quat *C*), 66.8 (CH_2O), 66.1 (CH_2O), 65.0 (CH_2O), 64.9 (CH_2O), 63.9 (CH_2O), 63.6 (CH_2O), 44.2 ($CHCH_3$), 42.8 ($CHCH_3$), 26.8 ($SiCMe_3$×2), 20.7 ($COCH_3$×2), 19.1 ($SiCMe_3$×2), 10.6 ($CHCH_3$), 7.8 ($CHCH_3$); *m*/*z* found 486.2357, 508.2161 (M+H$^+$, $C_{26}H_{36}O_6NSi$ requires 486.2312; M+Na, $C_{26}H_{35}O_6NSiNa$ requires 508.2131).

4.1.15. (3*R*,5*R*)-5-({[(1,1-Dimethylethyl)(diphenyl)-silyl]oxy}methyl)-5-(hydroxymethyl)-3-methyl-4-methylidene-2-pyrrolidinone (24). Titanium tetraisopropoxide (33 μL, 0.11 mmol) was added to a stirred solution of the acetoxypyrrolidinone **19** (10 mg, 0.022 mmol) in isopropanol (0.1 mL), and the mixture was stirred at room temperature for 3 h. The mixture was then diluted with water (2 mL) and ethyl acetate (2 mL) and the resulting colourless precipitate was then removed by filtration. The separated aqueous phase was extracted with ethyl acetate (3×2 mL) and the combined organic extracts were dried over $MgSO_4$ and evaporated in vacuo to leave the hydroxypyrrolidinone (8 mg, 89%) as a colourless oil; $[\alpha]_D^{24}$ 4.1 (*c* 1.6, $CHCl_3$); ν_{max} ($CHCl_3$) 3428, 2932, 2860, 1705 cm^{-1}; δ_H (360 MHz, $CDCl_3$) 7.65–7.62 (4H, m, Ar-*H*), 7.44–7.40 (6H, m, Ar-*H*), 6.13 (1H, s, N*H*), 5.10 (1H, d, *J*=2.9, CH_2=C), 5.07 (1H, d, *J*=2.9, CH_2=C), 3.89 (1H, d, *J*=11.3, CH_2OH), 3.74 (1H, d, *J*=10.2, CH_2O), 3.65 (1H, d, *J*=10.2, CH_2O), 3.56 (1H, d, *J*=11.3, CH_2OH), 3.06–3.03 (1H, m, $CHCH_3$), 1.32 (3H, d, *J*=7.4, $CHCH_3$), 1.06 (9H, s, $SiC(CH_3)_3$); δ_C (90 MHz, $CDCl_3$) 177.8 ($CONH$), 149.0 (*C*=CH_2), 135.6 (4×Ar-*C*H), 132.3 (2×Ar-*C*), 130.0 (4×Ar-*C*H), 127.9 (2×Ar-*C*H), 109.0 (C=*C*H_2), 77.0 (quat. *C*), 67.9 (CH_2O), 66.5 (CH_2O), 41.1 ($CHCH_3$), 26.8 ($SiCMe_3$), 19.2 ($SiCMe_3$), 15.8 ($CHCH_3$); *m*/*z* found 410.2138, 432.2014 (M+H$^+$, $C_{24}H_{32}O_3NSi$ requires 410.2151; M+Na, $C_{24}H_{31}O_2NSiNa$ requires 432.1971), which was used without further purification.

4.1.16. (5*R*)-5-({[(1,1-Dimethylethyl)(diphenyl)silyl]-oxy}methyl)-5-(hydroxymethyl)-3,4-dimethyl-1,5-dihydro-2*H*-pyrrol-2-one (25). Potassium carbonate (15 mg, 0.11 mmol) was added to a stirred solution of the pyrrolidinone **19** (25 mg, 0.055 mmol) in methanol (0.2 mL) and the suspension was stirred vigorously at room temperature for 15 h. The mixture was diluted with diethyl ether (5 mL), then filtered and the filtrate was concentrated in vacuo. The residue was purified by flash column chromatography, on silica gel, eluting with diethyl ether to give the dihydropyrrolone (16 mg, 80%) as a colourless oil; $[\alpha]_D^{24}$ −6.6 (*c* 2.0, $CHCl_3$); ν_{max} ($CHCl_3$) 3442, 2931, 2859, 1692, 1113 cm^{-1}; δ_H (360 MHz, $CDCl_3$) 7.72–7.68 (2H, m, Ar-*H*), 7.63–7.61 (3H, m, Ar-*H*), 7.44–7.40 (5H, m, Ar-*H*), 6.46 (1H, br s, N*H*), 3.93 (1H, dd, *J*=11.4 and 5.3, CH_2OH), 3.80 (1H, d, *J*=10.2, CH_2OSi), 3.65 (1H, d, *J*=10.2, CH_2OSi), 3.60 (1H, dd, *J*=11.4 and 7.7, CH_2OH), 2.76 (1H, dd, *J*=7.7 and 5.3, O*H*), 1.81 (3H, s, C=CCH_3), 1.76 (3H, s, C=CCH_3), 1.05 (9H, s, $SiC(CH_3)_3$); δ_C (90 MHz, $CDCl_3$) 174.8 ($CONH$), 152.2 (H_3CC=CCH_3), 135.6 (2×Ar-*C*H), 135.5 (2×Ar-*C*H), 133.5 (H_3CC=CCH_3), 132.5 (Ar-*C*), 132.4 (Ar-*C*), 130.0 (2×Ar-*C*H), 129.6 (2×Ar-*C*H), 127.9 (Ar-*C*H), 127.7 (Ar-*C*H), 68.9 (CH_2O), 65.6 (CH_2O), 63.6 (quat. *C*), 26.7 ($SiCMe_3$), 19.1 ($SiCMe_3$), 11.7 (CH_3C=C), 8.3 (CH_3C=C); *m*/*z* found 410.2152, 432.1976 (M+H$^+$, $C_{24}H_{31}O_3NSi$ requires 410.2151; M+Na, $C_{24}H_{30}O_2NSiNa$ requires 432.1971).

4.1.17. (3*R*,4*S*,5*R*)-5-({[(1,1-Dimethylethyl)(diphenyl)-silyl]oxy}methyl)-4-hydroxy-4,5-bis(hydroxymethyl)-3-methyl-2-pyrrolidinone (26). A solution of osmium tetroxide (0.2 M in dichloromethane, 0.71 mL, 0.14 mmol) was added to a stirred solution of the alcohol **24** (55 mg, 0.13 mmol) and *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (21 μL, 0.14 mmol) in dichloromethane (2.5 mL) at −78 °C under a nitrogen atmosphere. The resulting deep red solution was stirred at −78 °C for 1 h and then at room temperature for 2 h. The solvent was removed in vacuo and the residue was then diluted with acidic methanol (10 mL of methanol, two drops of concentrated hydrochloric acid). The mixture was stirred at room temperature for 4 h and then evaporated under reduced pressure. The residue was purified by flash column chromatography, on silica gel, eluting with ethyl acetate to give the pyrrolidinone (19 mg, 35%) as a pale brown oil; $[\alpha]_D^{24}$ −36.5 (*c* 0.8, $CHCl_3$); ν_{max} ($CHCl_3$) 3424, 2929, 2858, 1707 cm^{-1}; δ_H (360 MHz, $CDCl_3$) 7.67–7.62 (4H, m, Ar-*H*), 7.49–7.40 (6H, m, Ar-*H*), 5.71 (1H, s, N*H*), 3.88 (1H, d, *J*=11.0, CH_2O), 3.83 (1H, d, *J*=11.0, CH_2O), 3.72 (1H, d, *J*=10.7, CH_2O), 3.66 (1H, d, *J*=12.3, CH_2O), 3.64 (1H, d, *J*=10.7, CH_2O), 3.55 (1H, d, *J*=12.3, CH_2O), 3.40 (1H, br s, O*H*), 2.40 (1H, q, *J*=7.3, $CHCH_3$), 1.14 (3H, d, *J*=7.3, $CHCH_3$), 1.07 (9H, s, $SiC(CH_3)_3$); δ_C (125 MHz, CD_3OD) 180.0 ($CONH$), 138.3 (Ar-*C*H), 137.6 (Ar-*C*H), 134.8 (Ar-*C*), 134.7 (Ar-*C*), 131.9 (Ar-*C*H), 131.3 (Ar-*C*H), 129.8 (Ar-*C*H), 129.7 (Ar-*C*H), 82.7 (*C*(OH)), 70.2 (CH_2O), 67.5 (CH_2O), 65.6 (CH_2O), 64.4 (quat. *C*), 49.9 ($CHCH_3$), 28.1 ($SiCMe_3$), 21.1 ($SiCMe_3$), 9.1 ($CHCH_3$); *m*/*z* found 444.2245, 466.2067 (M+H$^+$, $C_{24}H_{34}O_5NSi$ requires 444.2206; M+Na, $C_{24}H_{33}O_5NSiNa$ requires 466.2026).

4.1.18. [(5*S*,6*R*,9*R*)-6-({[(1,1-Dimethylethyl)(diphenyl)-silyl]oxy}methyl)-2,2,9-trimethyl-8-oxo-1,3-dioxa-7-

azaspiro[4.4]non-6-yl]methyl 2,2-dimethylpropanoate (27). 2,2-Dimethoxypropane (53 μL, 0.43 mmol) was added to a stirred solution of the triol **26** (19 mg, 0.043 mmol) and *para*-toluenesulfonic acid (1 mg) in dichloromethane (0.25 mL) at room temperature. The mixture was stirred at room temperature for 3 h and then diluted with a saturated aqueous solution of sodium bicarbonate (0.5 mL). The organic phase was separated and the aqueous phase was then extracted with ethyl acetate (3×2 mL). The combined organic extracts were dried over $MgSO_4$ and evaporated in vacuo. The residue was purified by flash column chromatography, on silica gel, eluting with ethyl acetate to give the corresponding acetonide (10 mg, 48%) as a colourless oil; $[\alpha]_D^{24}$ 4.5 (*c* 0.4, $CHCl_3$); ν_{max} ($CHCl_3$) 3423, 2931, 1709 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.64–7.61 (4H, m, Ar-*H*), 7.49–7.41 (6H, m, Ar-*H*), 5.77 (1H, br s, N*H*), 4.28 (1H, d, *J*=10.0, CH_2O), 3.93 (1H, d, *J*=10.0, CH_2O), 3.82 (1H, d, *J*=11.6, CH_2OH), 3.66 (1H, dd, *J*=11.6 and 4.0, CH_2OH), 3.64 (1H, d, *J*=10.8, CH_2O), 3.57 (1H, d, *J*=10.8, CH_2O), 2.68 (1H, q, *J*=7.3, C*H*CH_3), 2.55 (1H, br s, O*H*), 1.48 (3H, s, CCH_3), 1.43 (3H, s, CCH_3), 1.20 (1H, d, *J*=7.3, CHCH_3), 1.06 (9H, s, SiC(CH_3)$_3$); δ_C (125 MHz, $CDCl_3$) 176.3 (*C*ONH), 135.6 (4×Ar-*C*H), 132.0 (Ar-*C*), 131.9 (Ar-*C*), 130.2 (4×Ar-*C*H), 128.0 (2×Ar-*C*H), 110.4 (*C*Me_2), 88.9 (*C*(O)), 67.8 (*C*H_2O), 66.3 (*C*H_2O), 65.2 (*C*H_2O), 62.3 (quat. *C*), 44.2 (*C*HCH_3), 29.7 (C*C*H_3), 26.8 (Si*CMe*$_3$), 25.6 (C*C*H_3), 19.1 (Si*C*Me_3), 9.0 (CH*C*H_3); *m/z* found 484.2521, 506.2339 (M+H^+, $C_{27}H_{38}O_5NSi$ requires 484.2519; M+Na, $C_{27}H_{37}O_5NSiNa$ requires 506.2339).

A solution of trimethylacetyl chloride (1 M in dichloromethane; 110 μL, 0.11 mmol) was added to a stirred solution of the acetonide (10 mg, 0.021 mmol) and *N*,*N*-dimethylaminopyridine (1 mg, 7 μmol) in dichloromethane/pyridine (1:1; 0.2 mL) at room temperature. The mixture was heated at 40 °C for 24 h and then diluted with water (1 mL) and dichloromethane (1 mL). The organic phase was separated and the aqueous phase was extracted with dichloromethane (3×2 mL). The combined organic extracts were dried over $MgSO_4$ and then evaporated in vacuo. The residue was purified by flash column chromatography, on silica gel, eluting with diethyl ether to give the pivalate ester (8 mg, 67%) as a colourless oil; $[\alpha]_D^{24}$ 20.0 (*c* 0.1, $CHCl_3$); ν_{max} ($CHCl_3$) 2962, 1707, 1092 cm^{-1}; δ_H (360 MHz, $CDCl_3$) 7.62–7.59 (4H, m, Ar-*H*), 7.44–7.40 (6H, m, Ar-*H*), 5.56 (1H, s, N*H*), 4.42 (1H, d, *J*=9.9, CH_2O), 4.22 (1H, d, *J*=11.4, CH_2O), 4.15 (1H, d, *J*=11.4, CH_2O), 4.04 (1H, d, *J*=9.9, CH_2O), 3.72 (1H, d, *J*=11.3, CH_2O), 3.62 (1H, d, *J*=11.3, CH_2O), 2.85 (1H, q, *J*=7.4, C*H*CH_3), 1.44 (6H, s, C(CH_3)$_2$), 1.22 (3H, d, *J*=7.4, CHCH_3), 1.03 (9H, s, SiC(CH_3)$_3$), 1.00 (9H, s, C(CH_3)$_3$); δ_C (125 MHz, $CDCl_3$) 176.6 (*C*ONH), 176.6 (*C*$OOCH_2$), 135.7 (2×Ar-*C*H), 135.5 (2×Ar-*C*H), 132.1 (2×Ar-*C*), 130.2 (Ar-*C*H), 130.1 (Ar-*C*H), 128.0 (4×Ar-*C*H), 110.5 (*C*Me_2), 87.7 (*C*(O)), 68.6 (quat. *C*), 65.3 (2×*C*H_2O), 65.2 (*C*H_2O), 45.0 (*C*HCH_3), 26.9 (2×C*C*H_3), 26.8 (Si*CMe*$_3$), 26.5 (*C*Me_3), 25.6 (C(*C*H_3)$_3$), 19.1 (Si*C*Me_3), 9.0 (CH*C*H_3); *m/z* found 568.3040, 590.2880 (M+H^+, $C_{32}H_{46}O_6NSi$ requires 568.3094; M+Na, $C_{32}H_{45}O_6NSiNa$ requires 590.2914).

4.1.19. Methyl (5*S*,6*R*,9*R*)-6-{[(2,2-dimethylpropanoyl)-oxy]methyl}-2,2,9-trimethyl-8-oxo-1,3-dioxa-7-azaspiro-[4.4]nonane-6-carboxylate (28b). Tetrabutylammonium fluoride (1 M in THF; 39 μL, 0.039 mmol) was added to a stirred solution of the pivalate ester **27** (11 mg, 0.019 mmol) in THF (0.2 mL) at room temperature. The mixture was stirred at room temperature for 1.5 h and then diluted with water (1 mL) and ethyl acetate (1 mL). The organic phase was separated and the aqueous phase was extracted with ethyl acetate (3×2 mL). The combined organic extracts were dried over $MgSO_4$ and evaporated in vacuo. The residue was purified by flash column chromatography, on silica gel, eluting with ethyl acetate to give a 3:1 mixture of diastereoisomers of the alcohols **28a** and **29a** (4 mg, 64%). A solution of sodium periodate (10 mg, 0.049 mmol) in water (0.15 mL) was added to a stirred solution of the alcohols (4 mg, 0.012 mmol) in acetonitrile (0.1 mL) and carbon tetrachloride (0.1 mL). After 5 min, $RuO_2 \cdot H_2O$ (1 mg, 7 μmol) was added and the biphasic mixture was then stirred vigorously for 5 h. A solution of trimethylsilyldiazomethane (2 M in hexanes; 30 μL, 0.17 mmol) was added and the solution was stirred for a further 1 h. The mixture was diluted with water (1 mL) and ethyl acetate (2 mL) and the organic phase was then separated. The aqueous phase was extracted with ethyl acetate (3×2 mL) and the combined organic extracts were dried over $MgSO_4$ and evaporated in vacuo. The residue was purified by flash column chromatography, on silica gel, eluting with ethyl acetate to give a 3:1 mixture of diastereoisomers of the esters **28b** and **29b** (4 mg, 91%) as a colourless oil. Further purification by flash column chromatography eluting with ethyl acetate gave the major diastereoisomer **28b** (1 mg, 23%) as an oil; $[\alpha]_D^{24}$ 1.5 (*c* 0.4, $CHCl_3$); ν_{max} ($CHCl_3$) 3429, 2955, 1713 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 6.07 (1H, s, N*H*), 4.53 (1H, d, *J*=11.2, CH_2O), 4.45 (1H, d, *J*=9.7, CH_2O), 4.08 (1H, d, *J*=11.2, CH_2O), 4.04 (1H, d, *J*=9.7, CH_2O), 3.80 (3H, s, CO_2CH_3), 2.52 (1H, q, *J*=7.3, C*H*CH_3), 1.45 (6H, s, CCH_3), 1.31–1.20 (3H, m, CHCH_3), 1.15 (9H, s, C(CH_3)$_3$); *m/z* (LCMS, EI) 371.23 (M+Na^+, $C_{17}H_{28}O_7NNa$ requires 371.1866); ROESY experiment (700 MHz, $CDCl_3$) δ_H 4.66 correlates to δ_H 4.08 and δ_H 4.04.

4.1.20. (*R*)-4-(*tert*-Butyl-dimethyl-silanyloxymethyl)-4-ethynyl-2-trichloromethyl-4,5-dihydro-oxazole (30). *tert*-Butyldimethylsilyl chloride (4.40 g, 29.1 mmol) was added portionwise over 10 min to a stirred solution of the oxazoline **16a** (5.43 g, 22.4 mmol) and imidazole (2.30 g, 33.6 mmol) in dichloromethane (110 mL). The mixture was stirred at room temperature for 15 h and then diluted with water (50 mL). The organic phase was separated and the aqueous phase was extracted with dichloromethane (3×50 mL). The combined organic extracts were dried over $MgSO_4$ and evaporated in vacuo. The residue was purified by flash column chromatography, on silica gel, eluting with pentane/ether (9:1) to give the TBS ether (6.62 g, 83%) as a colourless solid; mp 61–62 °C; $[\alpha]_D^{24}$ −0.38 (*c* 1.05, $CHCl_3$); Found: C, 43.6; H, 5.6; N, 3.8; $C_{13}H_{20}O_2NSiCl_3$ requires C, 43.9; H, 5.7; N, 3.9%; ν_{max} ($CHCl_3$) 3306, 2955, 2930, 2859 cm^{-1}; δ_H (360 MHz, $CDCl_3$) 4.85 (1H, d, *J*=8.1, CH_2O), 4.61 (1H, d, *J*=8.1, CH_2O), 3.94 (1H, d, *J*=10.4, CH_2O), 3.74 (1H, d, *J*=10.4, CH_2O), 2.56 (1H, s, C≡C*H*), 0.90 (9H, s, SiC(CH_3)$_3$), 0.09 (6H, s, 2×SiCH_3); δ_C (90 MHz, $CDCl_3$) 164.1 (*C*═N), 81.5 (quat. *C*), 77.4 (*C*H_2O), 76.6 (*C*≡CH), 74.8 (C≡*C*H), 70.0 (*C*Cl_3), 67.0 (*C*H_2OH), 25.7 (Si*CMe*$_3$), 18.2 (Si*C*Me_3), −5.3 (Si*C*H_3), −5.6 (Si*C*H_3); *m/z* (EI) found 356.0421,

358.0395 (M+H$^+$, $C_{13}H_{21}O_2NSiCl_3$ requires 356.0407; $C_{13}H_{21}O_2NSiCl_2{}^{37}Cl$ requires 358.0378).

4.1.21. 2-Bromo-*N*-[(*S*)-1-(*tert*-butyl-dimethyl-silanyloxymethyl)-1-hydroxymethyl-prop-2-ynyl]propionamide (32). Aqueous hydrochloric acid (1 M, 16.0 mL, 16.0 mmol) was added in a single portion to a stirred solution of the oxazoline **30** (5.7 g, 16.0 mmol) in THF (94 mL) at room temperature. The mixture was stirred at room temperature for 3 h and then a saturated aqueous solution of sodium bicarbonate (~13 mL) was added until the mixture was pH 7. The solvent was evaporated in vacuo to leave the amine **31**, which was immediately suspended in dichloromethane (9.4 mL), water (18.2 mL) and a saturated aqueous solution of sodium bicarbonate (66.8 mL). 2-Bromopropionoyl chloride (1.60 mL, 16.0 mmol) was added dropwise over 5 min to the biphasic mixture, which was then stirred vigorously for 2 h. The mixture was diluted with dichloromethane (10 mL), and the separated aqueous phase was then extracted with dichloromethane (2×20 mL) and ethyl acetate (1×20 mL). The combined organic extracts were dried over $MgSO_4$ and evaporated in vacuo. The residue was purified by flash column chromatography, on silica gel, eluting with pentane/ether (1:1) to give a 1:1 mixture of diastereoisomers of the amide (4.2 g, 72%) as a colourless oil; $[\alpha]_D^{24}$ −5.8 (*c* 1.4, $CHCl_3$); Found: C, 46.4; H, 7.2; N, 4.0; $C_{14}H_{26}O_3NBrSi$ requires C, 46.3; H, 7.2; N, 3.9%; ν_{max} ($CHCl_3$) 3388, 3306, 2954, 2930, 2859, 1674 cm^{-1}; δ_H (360 MHz, $CDCl_3$) 7.20 (2H, br s, N*H*), 4.41 (2×1H, q, *J*=7.1, C*H*BrCH$_3$), 3.98 (1H, d, *J*=9.9, CH_2O) 3.96 (1H, d, *J*=9.9, CH_2O), 3.92 (2×1H, dd, *J*=11.4 and 4.1, CH_2OH), 3.87 (1H, d, *J*=9.9, CH_2O), 3.86 (1H, d, *J*=9.9, CH_2O), 3.83–3.79 (2H, m, CH_2OH), 3.49–3.45 (2H, m, O*H*), 2.44 (2H, s, 2×C≡C*H*), 1.88 (2×3H, d, *J*=7.1, CH_3CHBr), 0.92 (18H, s, SiC(CH_3)$_3$), 0.12 (12H, s, 2×SiCH_3); δ_C (90 MHz, $CDCl_3$) 169.2 (*C*ONH), 169.1 (*C*ONH), 80.2 (C≡*C*H), 77.2 (C≡*C*H), 73.6 (*C*≡CH), 73.6 (*C*≡CH), 65.9 (2×*C*H$_2$O), 65.7 (*C*H$_2$O), 65.5 (*C*H$_2$O), 56.5 (quat. *C*), 56.4 (quat. *C*), 44.8 (*C*HBrCH$_3$), 44.7 (*C*HBrCH$_3$), 25.6 (2×SiC*Me*$_3$), 22.9 (CHBr*C*H$_3$), 22.7 (CHBr*C*H$_3$), 18.0 (2×SiCMe$_3$), −5.6 (2×Si*C*H$_3$), −5.7 (2×Si*C*H$_3$); *m*/*z* (FAB) found 364.0945, 366.0932 (M+H$^+$, $C_{14}H_{27}O_3N^{79}BrSi$ requires 364.0944; $C_{14}H_{27}O_3N^{81}BrSi$ requires 366.0923).

4.1.22. 2-Bromo-*N*-[(*S*)-1-(*tert*-butyl-dimethyl-silanyloxymethyl)-1-formyl-prop-2-ynyl]propionamide (33a). Tetrapropylammonium perrutherate (0.20 g, 0.58 mmol) was added to a stirred solution of the 1:1 mixture of diastereoisomers of the amide **32** (4.20 g, 11.6 mmol), *N*-methylmorpholine-*N*-oxide (2.30 g, 23.2 mmol) and powdered 3 Å molecular sieves (6.0 g) in dichloromethane (60 mL) at room temperature. The suspension was stirred at room temperature for 1 h, and then a second portion of tetrapropylammonium perrutherate (0.20 g, 0.58 mmol) was added. The suspension was stirred for a further 1 h and then filtered through a pad of silica gel, eluting with diethyl ether. The filtrate was evaporated in vacuo to leave a 1:1 mixture of diastereoisomers of the aldehyde (3.7 g, 88%) as a yellow oil; $[\alpha]_D^{24}$ 21.4 (*c* 1.6, $CHCl_3$); ν_{max} ($CHCl_3$) 3390, 3304, 2955, 2930, 2859, 1746, 1678, 1116 cm^{-1}; δ_H (360 MHz, $CDCl_3$) 9.36 (2H, s, 2×C*H*O), 7.37 (2H, br s, 2×N*H*), 4.47–4.42 (2H, m, 2×C*H*BrCH$_3$), 4.19 (1H, d, *J*=8.7, CH_2O), 4.16 (1H, d, *J*=8.7, CH_2O), 4.08 (1H, d, *J*=10.3, CH_2O), 4.07 (1H, d, *J*=10.3, CH_2O), 2.61 (2H, s, 2×C≡C*H*), 1.89 (3H, d, *J*=7.1, CH_3BrCH), 1.88 (3H, d, *J*=7.0, CH_3BrCH), 0.87 (18H, s, 2×SiC(CH_3)$_3$), 0.06 (12H, s, 4×SiCH_3); δ_C (90 MHz, $CDCl_3$) 191.5 (*C*HO), 191.4 (*C*HO), 168.8 (*C*ONH), 168.7 (*C*ONH), 76.5 (*C*≡CH), 76.4 (*C*≡CH), 76.0 (2×C≡*C*H), 64.1 (*C*H$_2$O), 64.0 (*C*H$_2$O), 62.0 (2×quat. *C*), 44.0 (2×*C*HBrCH$_3$), 25.7 (SiC*Me*$_3$), 25.6 (SiC*Me*$_3$), 22.8 (*C*H$_3$BrCH), 22.7 (*C*H$_3$BrCH), 18.0 (2×SiCMe$_3$), −5.6 (4×Si*C*H$_3$); *m*/*z* (CI, NH_4^+) found 362.0784, 364.0772 (M$^+$ $C_{14}H_{25}O_3N^{79}BrSi$ requires 362.0787; $C_{14}H_{25}O_3N^{81}BrSi$ requires 364.0767).

4.1.23. (*R*)-2-(2-Bromo-propionylamino)-2-(*tert*-butyl-dimethyl-silanyloxymethyl)-but-3-ynoic acid (33b). A solution of sodium chlorite (3.36 g, 37.0 mmol) and sodium hydrogen orthophosphate (4.39 g, 28.5 mmol) in water (8 mL) was added in a single portion to a stirred solution of a 1:1 mixture of diastereoisomers of the aldehyde **33a** (1.34 g, 3.70 mmol) in *tert*-butanol (20 mL) and 2-methyl-2-butene (8 mL). The solution was stirred at room temperature for 6 h, and then diluted with ethyl acetate (20 mL). The organic phase was separated, and then the aqueous phase extracted with ethyl acetate (5×20 mL). The combined organic extracts were dried over $MgSO_4$ and evaporated in vacuo to leave a 1:1 mixture of diastereoisomers of the carboxylic acid (1.16 g, 83%) as a colourless oil; $[\alpha]_D^{24}$ +1.5 (*c* 1.9, $CHCl_3$); ν_{max} ($CHCl_3$) 3383, 3306, 2930, 2858, 1731, 1680, 1104 cm^{-1}; δ_H (360 MHz, $CDCl_3$) 7.52 (2H, br s, 2×NH), 4.49–4.44 (2H, m, 2×C*H*BrCH$_3$), 4.22–4.15 (4H, m, 2×CH_2O), 2.54 (2H, s, 2×C≡C*H*), 1.91 (3H, d, *J*=7.1, CH_3BrCH), 1.90 (3H, d, *J*=7.1, CH_3BrCH), 0.90 (18H, s, 2×SiC(CH_3)$_3$), 0.10 (12H, s, 4×SiCH_3); δ_C (90 MHz, $CDCl_3$) 170.3 (*C*O$_2$H), 170.2 (*C*O$_2$H), 169.4 (*C*ONH), 169.4 (*C*ONH), 77.2 (2×*C*≡CH), 74.1 (2×C≡*C*H), 66.1 (CH_2O), 65.9 (CH_2O), 58.4 (quat. *C*), 58.3 (quat. *C*), 44.4 (*C*HBrCH$_3$), 44.2 (*C*HBrCH$_3$), 25.6 (2×SiC*Me*$_3$), 22.9 (*C*H$_3$BrCH), 22.7 (*C*H$_3$BrCH), 18.1 (2×SiCMe$_3$), −5.5 (2×Si*C*H$_3$), −5.6 (2×Si*C*H$_3$); *m*/*z* (ES) found 378.0770, 380.0733 (M+H$^+$, $C_{14}H_{25}O_4N^{79}BrSi$ requires 3378.0736; $C_{14}H_{25}O_4N^{81}BrSi$ requires 380.0716), which was used without further purification.

4.1.24. (*R*)-2-(2-Bromo-propionylamino)-2-(*tert*-butyl-dimethyl-silanyloxymethyl)-but-3-ynoic acid methyl ester (34). A solution of trimethylsilyldiazomethane (2 M in diethyl ether; 5 mL, 10 mmol) was added dropwise over 10 min to a stirred solution of a 1:1 mixture of diastereoisomers of the acid **33b** (1.25 g, 3.31 mmol) in benzene/methanol (5:2, 17 mL) at room temperature. The solution was stirred at room temperature for 1 h, and then the solvent was evaporated in vacuo. The residue was purified by flash column chromatography, on silica gel, eluting with pentane/ether (1:1) to give a 1:1 mixture of diastereoisomers of the methyl ester (0.96 g, 75%) as a yellow oil; $[\alpha]_D^{24}$ −2.8 (*c* 1.0, $CHCl_3$); ν_{max} ($CHCl_3$) 3390, 3306, 2955, 2930, 2858, 1749 cm^{-1}; δ_H (360 MHz, $CDCl_3$) 7.46 (2H, br s, 2×N*H*), 4.47–4.43 (2H, m, 2×C*H*BrCH$_3$), 4.29 (1H, d, *J*=9.7, CH_2O), 4.25 (1H, d, *J*=9.7, CH_2O), 4.07 (1H, *J*=6.3, CH_2O), 4.05 (1H, d, *J*=6.2, CH_2O), 3.87 (6H, s, 2×CO$_2$CH_3), 2.52 (2H, s, 2×C≡C*H*), 1.92 (3H, d, *J*=7.1, CH_3BrCH), 1.91 (3H, d, *J*=7.1, CH_3BrCH), 0.89 (18H, s, 2×SiC(CH_3)$_3$), 0.08 (12H, s, 4×SiCH_3); δ_C (90 MHz,

$CDCl_3$) 168.4 (*C*ONH), 168.3 (*C*ONH), 168.1 (*C*O_2CH_3), 168.0 (*C*O_2CH_3), 77.4 (2×*C*≡CH), 73.6 (2×C≡*C*H), 66.2 (CH_2O), 66.0 (CH_2O), 58.7 (quat. *C*), 58.7 (quat. *C*), 53.7 (2×CO_2CH_3), 44.5 (*C*HBrCH_3), 44.4 (*C*HBrCH_3), 25.5 (2×SiCMe_3), 22.9 (*C*H_3BrCH), 22.8 (*C*H_3BrCH), 18.0 (2×SiCMe_3), −5.5 (2×Si*C*H_3), −5.7 (2×Si*C*H_3); *m/z* (CI, NH_4^+) found 392.0889, 394.0876 (M+H^+, $C_{15}H_{26}O_4N^{79}$BrSi requires 392.0892; $C_{15}H_{26}O_4N^{81}$BrSi requires 394.0872).

4.1.25. (*R*)-2-(*tert*-Butyl-dimethyl-silanyloxymethyl)-4-methyl-3-methylene-5-oxo-pyrrolidine-2-carboxylic acid methyl ester (35a). A solution of tributyltin hydride (0.60 mL, 2.24 mmol) and AIBN (67 mg, 0.41 mmol) in degassed toluene (60 mL) was added dropwise over 0.5 h, via syringe pump, to a refluxing solution of a 1:1 mixture of diastereoisomers of the amide **34** (0.80 g, 2.04 mmol) in degassed toluene (680 mL) under an atmosphere of argon. The solution was heated under reflux for 2 h and then allowed to cool to room temperature before the solvent was evaporated in vacuo. The residue was partitioned between acetonitrile (50 mL) and hexane (50 mL). The acetonitrile phase was separated and the hexane phase was extracted with acetonitrile (50 mL). The combined acetonitrile extracts were evaporated in vacuo and the residue was purified by flash column chromatography, on silica gel, eluting with pentane/diethyl ether (7:3) then diethyl ether to give a 2:1 mixture of β- and α-methyl epimers of the pyrrolidinone (0.47 g, 73%) as a colourless oil; $[\alpha]_D^{24}$ +9.0 (*c* 0.8, $CHCl_3$); Found: C, 57.8; H, 8.4; N, 4.2; $C_{15}H_{27}O_4NSi$ requires C, 57.5; H, 8.7; N, 4.5%; ν_{max} ($CHCl_3$) 3435, 2954, 2930, 2858, 1745, 1712, 1662, 1097 cm^{-1}; δ_H (360 MHz, $CDCl_3$) 6.24 (1H, br s, N*H*), 6.21 (1H, br s, N*H*), 5.51 (1H, d, *J*=2.8, C=CH_2), 5.44 (1H, d, *J*=2.9, C=CH_2), 5.20 (2H, m, 2×C=CH_2), 4.23 (1H, d, *J*=9.4, CH_2O), 4.15 (1H, d, *J*=9.4, CH_2O), 3.77 (3H, s, CO_2CH_3), 3.76 (3H, s, CO_2CH_3), 3.55 (1H, d, *J*=9.4, CH_2O), 3.47 (1H, d, *J*=9.4, CH_2O), 3.08–3.02 (2H, m, 2×C*H*CH_3), 1.31 (6H, d, *J*=7.4, 2×CH_3CH), 0.87 (18H, s, 2×SiC(CH_3)$_3$), 0.07 (12H, s, 4×SiCH_3); δ_C (90 MHz, $CDCl_3$) 177.0 (CO_2CH_3), 176.9 (CO_2CH_3), 171.2 (*C*ONH), 171.1 (*C*ONH), 145.2 (*C*=CH_2), 145.1 (*C*=CH_2), 111.6 (C=*C*H_2), 111.4 (C=*C*H_2), 70.0 (quat. *C*), 69.5 (2×CH_2O), 52.9 (2×CO_2CH_3), 40.4 (*C*HCH_3), 40.2 (*C*HCH_3), 25.6 (2×SiCMe_3), 18.1 (2×SiCMe_3), 16.4 (CH*C*H_3), 15.7 (CH*C*H_3), −5.5 (2×Si*C*H_3), −5.7 (2×Si*C*H_3); *m/z* (CI, NH_4^+) 314.1771 (M+H^+, $C_{15}H_{28}O_4NSi$ requires 314.1756).

4.1.26. (2*R*,4*R*)-2-Hydroxymethyl-4-methyl-3-methylene-5-oxo-pyrrolidine-2-carboxylic acid methyl ester (35b) and (2*R*,4*S*)-2-hydroxymethyl-4-methyl-3-methylene-5-oxo-pyrrolidine-2-carboxylic acid methyl ester (36b). *para*-Toluenesulfonic acid (1.04 g, 5.44 mmol) was added to a stirred solution of a 2:1 mixture of C3-methyl epimers of the pyrrolidinone **36a** (0.57 g, 1.82 mmol) in THF/H_2O (20:1, 10 mL) at room temperature. The mixture was stirred at room temperature for 15 h and then diluted with a saturated aqueous solution of sodium bicarbonate (10 mL) and ethyl acetate (10 mL). The organic phase was separated, and then the aqueous phase was extracted with ethyl acetate (3×20 mL). The combined organic extracts were dried over $MgSO_4$ and evaporated in vacuo. The residue was purified by flash column chromatography, on silica gel, eluting with diethyl ether to give: (i) the β-methyl epimer **35b** (eluted first) (0.14 g, 39%) as a colourless oil; $[\alpha]_D^{24}$ +2.7 (*c* 0.3, $CHCl_3$); ν_{max} ($CHCl_3$) 2926, 1715, 1044 cm^{-1}; δ_H (360 MHz, $CDCl_3$) 6.77 (1H, br s, N*H*), 5.41 (1H, d, *J*=2.9, C=CH_2), 5.23 (1H, d, *J*=2.5, C=CH_2), 4.26 (1H, d, *J*=11.2, CH_2OH), 3.80 (3H, s, CO_2CH_3), 3.58 (1H, d, *J*=11.2, CH_2OH), 3.15–3.07 (1H, m, C*H*CH_3), 2.24 (1H, br s, O*H*), 1.31 (3H, d, *J*=7.4, CH_3CH); δ_C (90 MHz, $CDCl_3$) 177.9 (CO_2CH_3), 171.4 (*C*ONH), 145.5 (*C*=CH_2), 111.4 (C=*C*H_2), 69.8 (quat. *C*), 68.3 (CH_2O), 53.3 (CO_2CH_3), 40.4 (*C*HCH_3), 15.6 (CH*C*H_3); *m/z* (CI, NH_4^+) found 199.0828 (M^+, $C_9H_{13}O_4N$ requires 199.0845) and (ii) the α-methyl epimer **36b** (eluted second) (94 mg, 26%) as a colourless oil; $[\alpha]_D^{24}$ −22.0 (*c* 1.6, $CHCl_3$); ν_{max} ($CHCl_3$) 3428, 2955, 2877, 1713 cm^{-1}; δ_H (360 MHz, $CDCl_3$) 7.46 (1H, br s, N*H*), 5.46 (1H, d, *J*=2.8, C=CH_2), 5.20 (1H, d, *J*=2.3, C=CH_2), 4.16–4.11 (2H, m, CH_2OH and O*H*), 3.79 (3H, s, O*C*H_3), 3.68 (1H, dd, *J*=9.8 and 4.9, CH_2OH), 3.09–3.02 (1H, m, C*H*CH_3), 1.29 (3H, d, *J* 7.4, CH_3CH); δ_C (90 MHz, $CDCl_3$) 178.7 (CO_2CH_3), 171.3 (*C*ONH), 145.5 (*C*=CH_2), 111.4 (C=*C*H_2), 70.6 (quat. *C*), 68.3 (CH_2O), 53.2 (CO_2CH_3), 40.6 (*C*HCH_3), 16.3 (CH*C*H_3); *m/z* (CI, NH_4^+) found 199.0843 (M^+, $C_9H_{13}O_4N$ requires 199.0845).

4.1.27. (2*S*,3*S*,4*R*)-3-Hydroxy-2,3-bis-hydroxymethyl-4-methyl-5-oxo-pyrrolidine-2-carboxylic acid methyl ester (37). A solution of osmium tetroxide (0.2 M in dichloromethane, 2.6 mL, 0.52 mmol) was added dropwise over 5 min to a stirred solution of the alcohol **35b** (98 mg, 0.49 mmol) and *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (81 μL, 0.54 mmol) in dichloromethane (8 mL) at −78 °C under a nitrogen atmosphere. The resulting deep red solution was stirred at −78 °C for 1 h and then at room temperature for 2 h. The solvent was evaporated under reduced pressure and the residue was then diluted with acidic methanol (10 mL of methanol, four drops of concentrated hydrochloric acid). The mixture was stirred at room temperature for 3 h and then evaporated in vacuo. The residue was purified by flash column chromatography, on silica gel, eluting with ethyl acetate/methanol (4:1) to give the triol (114 mg, 99%) as an oil; $[\alpha]_D^{24}$ +19.4 (*c* 1.3, MeOH); ν_{max} ($CHCl_3$) 3630, 2943, 2838, 1715, 1011 cm^{-1}; δ_H (360 MHz, CD_3OD) 4.04 (1H, d, *J*=11.0, CH_2OH), 3.80 (1H, d, *J*=11.0, CH_2OH), 3.78 (1H, d, *J*=11.4, CH_2OH), 3.78 (3H, s, CO_2CH_3), 3.71 (1H, d, *J*=11.4, CH_2OH), 2.60 (1H, q, *J*=7.6, C*H*CH_3), 1.26 (3H, d, *J*=7.6, C*H*CH_3); δ_C (90 MHz, CD_3OD) 180.9 (*C*ONH), 172.4 (CO_2CH_3), 81.3 (*C*(OH)), 75.8 (quat. *C*), 63.9 (CH_2OH), 62.4 (CH_2OH), 52.7 (CO_2CH_3), 49.2 (C*H*CH_3), 11.3 (CHCH_3); *m/z* (ES) found 297.1040 (M+Na+CH_3CN, $C_9H_{15}O_6NCH_3CNNa$ requires 297.1063); In a ^{1}H NOE experiment (400 MHz, CD_3OD), irradiation at δ 2.60 (C*H*CH_3) gave an enhancement at δ 3.78 (CO_2CH_3); irradiation at δ 1.26 (CHCH_3) gave enhancements at δ 3.78 (CH_2OH) and 3.71 (CH_2OH).

4.1.28. (3*R*,3*S*,8*S*)-3a-Hydroxy-3,6,6-trimethyl-2-oxo-tetrahydro-5,7-dioxa-1-aza-azulene-8a-carboxylic acid methyl ester (40). 2,2-Dimethoxypropane (0.33 mL, 2.64 mmol) was added to a stirred solution of the diol **37** (77 mg, 0.33 mmol) and *para*-toluenesulfonic acid (1 mg) in dichloromethane (3 mL) at room temperature. The mixture was stirred at room temperature for 3 h and then diluted

with a saturated aqueous solution of sodium bicarbonate (5 mL) and ethyl acetate (5 mL). The organic phase was separated and the aqueous phase was then extracted with ethyl acetate (3×5 mL). The combined organic extracts were dried over $MgSO_4$ and then evaporated in vacuo. The residue was purified by flash column chromatography, on silica gel, eluting with ethyl acetate gave the acetonide (30 mg, 33%) as a colourless oil; $[\alpha]_D^{24}$ 7.7 (*c* 0.3, $CHCl_3$); ν_{max} ($CHCl_3$) 3425, 2958, 1719 cm^{-1}; δ_H (360 MHz, $CDCl_3$) 6.15 (1H, br s, N*H*), 4.50 (1H, d, *J*=14.3, CH_2O), 3.97 (1H, d, *J*=12.8, CH_2O), 3.78 (3H, s, CO_2CH_3), 3.62 (1H, d, *J*=14.3, CH_2O), 3.49 (1H, d, *J*=12.8, CH_2O), 3.34 (1H, s, O*H*), 2.95 (1H, q, *J*=7.6, C*H*CH_3), 1.43 (3H, s, C(CH_3)$_2$), 1.35 (3H, s, C(CH_3)$_2$), 1.09 (3H, d, *J*=7.6, CHCH_3); δ_C (90 MHz, $CDCl_3$) 176.7 (*C*ONH), 171.0 (*C*O_2CH_3), 110.2 (*C*Me_2), 81.1 (*C*(O)), 70.4 (quat. *C*), 63.1 (CH_2O), 59.4 (CH_2O), 52.8 (CO_2CH_3), 42.8 (C*H*CH_3), 24.5 (C*C*H_3), 23.8 (C*C*H_3), 7.3 (CHCH_3); these assignments were confirmed by a HMQC experiment; in an HMBC experiment (400 MHz, $CDCl_3$) δ_H 4.50 correlated to δ_C 110.2; δ_H 3.97 correlated to δ_C 110.2; δ_H 3.62 correlated to δ_C 110.2, 81.1 and 70.4; δ_H 3.49 correlates to δ_C 110.2, 81.1 and 70.4; *m/z* (CI, NH_4^+) found 274.1286 ($M+H^+$, $C_{12}H_{20}O_6N$ requires 274.1291).

4.1.29. (5*S*,6*S*,9*R*)-6-Hydroxymethyl-2,2,9-trimethyl-8-oxo-1,3-dioxa-7-aza-spiro[4.4]nonane-6-carboxylic acid methyl ester (39). 2,2-Dimethoxypropane (0.40 mL, 3.4 mmol) was added to a stirred solution of the diol **37** (80 mg, 0.34 mmol) and *para*-toluenesulfonic acid (13 mg, 0.07 mmol) in dichloromethane (2 mL) at room temperature. The mixture was stirred at room temperature for 15 h and then diluted with a saturated aqueous solution of sodium bicarbonate (5 mL) and ethyl acetate (5 mL). The organic phase was separated and the aqueous phase was then extracted with ethyl acetate (3×5 mL). The combined organic extracts were dried over $MgSO_4$ and evaporated in vacuo. The residue was purified by flash column chromatography, on silica gel, eluting with ethyl acetate to give the acetonide (36 mg, 39%) as a colourless oil; $[\alpha]_D^{24}$ 9.8 (*c* 1.0, $CHCl_3$); ν_{max} ($CHCl_3$) 3421, 2955, 1713, 1060 cm^{-1}; δ_H (360 MHz, $CDCl_3$) 7.33 (1H, br s, N*H*), 4.13 (2H, s, CH_2O), 4.04 (1H, d, *J*=11.7, CH_2O), 3.80 (3H, s, CO_2CH_3), 3.77 (1H, app. d, *J*=11.7, CH_2O), 2.95 (1H, q, *J*=7.8, C*H*CH_3), 1.39 (3H, s, C(CH_3)$_2$), 1.34 (3H, s, C(CH_3)$_2$), 1.21 (3H, d, *J*=7.8, CHCH_3); δ_C (100 MHz, $CDCl_3$) 178.0 (*C*ONH), 170.1 (*C*O_2CH_3), 110.1 (*C*Me_2), 87.3 (*C*(O)), 72.5 (quat. *C*), 64.8 (CH_2O), 64.0 (CH_2O), 52.8 (CO_2CH_3), 46.0 (C*H*CH_3), 27.0 (C*C*H_3), 25.6 (C*C*H_3), 11.1 (CHCH_3), these assignments were confirmed by a HMQC experiment; In a HMBC experiment (400 MHz, $CDCl_3$) δ_H 4.13 correlated to δ_C 110.1, 72.5 and 46.0; In a ^1H NOE experiment (400 MHz, $CDCl_3$), irradiation at δ 1.21 gave enhancements at δ 4.04 and 3.77; *m/z* (CI, NH_4^+) found 274.1287 ($M+H^+$, $C_{12}H_{20}O_6N$ requires 274.1291).

4.1.30. (5*S*,6*S*,9*R*)-6-(2,2-Dimethyl-propionyloxymethyl)-2,2,9-trimethyl-8-oxo-1,3-dioxa-7-aza-spiro[4.4]nonane-6-carboxylic acid methyl ester (41b). A solution of trimethylacetyl chloride (1 M in dichloromethane; 0.2 mL, 0.2 mmol) was added to a stirred solution of the alcohol **39** (18 mg, 0.066 mmol) and *N*,*N*-dimethylaminopyridine (1 mg, 7 μmol) in dichloromethane/pyridine (1:1; 0.2 mL) at room temperature. The mixture was heated at 40 °C for 24 h, and then diluted with water (1 mL) and dichloromethane (1 mL). The organic phase was separated and the aqueous phase was extracted with dichloromethane (3×2 mL). The combined organic extracts were dried over $MgSO_4$ and then evaporated in vacuo. The residue was purified by flash column chromatography, on silica gel, eluting with diethyl ether to give the pivalate ester (12 mg, 67%) as a colourless oil; $[\alpha]_D^{24}$ −1.0 (*c* 0.2, $CHCl_3$); ν_{max} ($CHCl_3$) 2923, 1729, 1098 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 6.36 (1H, br s, N*H*), 4.77 (1H, d, *J*=10.9, CH_2O), 4.15 (1H, d, *J*=9.8, CH_2O), 4.07 (1H, d, *J*=9.8, CH_2O), 4.02 (1H, d, *J*=10.9, CH_2O), 3.79 (3H, s, CO_2CH_3), 2.87 (1H, q, *J*=7.8, C*H*CH_3), 1.40 (6H, s, 2×C(CH_3)$_2$), 1.23 (3H, d, *J*=7.8, CHCH_3), 1.17 (9H, s, C(CH_3)$_3$); δ_C (100 MHz, $CDCl_3$) 177.5 (*C*OC(CH_3)$_3$), 176.4 (*C*ONH), 169.2 (*C*O_2CH_3), 110.4 (*C*Me_2), 87.5 (*C*(O)), 69.8 (quat. *C*), 65.4 (CH_2O), 64.6 (CH_2O), 52.8 (CO_2CH_3), 44.1 (C*H*CH_3), 38.8 (*C*Me_3), 27.1 (C*Me*$_3$), 27.0 (C*C*H_3), 25.6 (C*C*H_3), 11.0 (CHCH_3); these assignments were confirmed by a HMQC experiment; *m/z* (ES) found 358.1835 ($M+H^+$, $C_{17}H_{28}O_7N$ requires 358.1866).

4.1.31. (5*S*,6*S*,9*R*)-2,2,9-Trimethyl-8-oxo-6-(2-trimethylsilanyl-ethoxymethoxymethyl)-1,3-dioxa-7-aza-spiro-[4.4]nonane-6-carboxylic acid methyl ester (41a). [2-(Trimethylsilyl)ethoxy]methyl chloride (19 μL, 0.11 mmol) was added to a stirred solution of the acetonide **39** (15 mg, 0.055 mmol), tetrabutylammonium iodide (45 mg, 0.12 mmol) and diisopropylethylamine (28 μL, 0.22 mmol) in dichloromethane (0.3 mL) at room temperature. The mixture was stirred at room temperature for 15 h and then diluted with water (0.2 mL) and dichloromethane (0.2 mL). The organic phase was separated and the aqueous phase was extracted with dichloromethane (3×0.5 mL). The combined organic extracts were dried over $MgSO_4$ and evaporated in vacuo. The residue was purified by flash column chromatography, on silica gel, eluting with diethyl ether and then ethyl acetate to give the SEM ether (5 mg, 23%) as a colourless oil; $[\alpha]_D^{24}$ 2.0 (*c* 0.4, $CHCl_3$); ν_{max} ($CHCl_3$) 2923, 1714, 1099, 1059 cm^{-1}; δ_H (360 MHz, $CDCl_3$) 6.19 (1H, br s, N*H*), 4.64 (2H, s, OCH_2O), 4.16 (1H, d, *J*=9.1, CH_2O), 4.12 (1H, d, *J*=9.6, CH_2O), 4.06 (1H, d, *J*=9.6, CH_2O), 3.80 (3H, s, CO_2CH_3), 3.57 (2H, t, *J*=8.2, OCH_2CH_2Si), 3.53 (1H, d, *J*=9.1, CH_2O), 2.81 (1H, q, *J*=7.7, C*H*CH_3), 1.40 (3H, s, C(CH_3)$_2$), 1.38 (3H, s, C(CH_3)$_2$), 1.25 (3H, d, *J*=7.7, CHCH_3), 0.94 (2H, t, *J*=8.2, OCH$_2$CH_2Si), 0.04 (9H, s, Si(CH_3)$_3$); δ_C (90 MHz, $CDCl_3$) 176.4 (*C*ONH), 169.7 (*C*O_2CH_3), 110.3 (*C*Me_2), 95.2 (OCH_2O), 87.4 (*C*(O)), 70.6 (quat. *C*), 69.6 (CH_2O), 65.7 (CH_2O), 64.6 (CH_2O), 52.7 (CO_2CH_3), 45.0 (C*H*CH_3), 27.1 (C*C*H_3), 25.6 (C*C*H_3), 18.0 (OCH$_2$CH_2Si), 11.3 (CHCH_3), −1.4 (Si(CH_3)$_3$); *m/z* (EI) found 426.1935 (M+Na, $C_{18}H_{32}O_7NSi$ requires 426.1924).

4.1.32. (5*S*,6*S*,9*R*)-2,2,7,9-Tetramethyl-8-oxo-6-(2-trimethylsilanyl-ethoxymethoxymethyl)-1,3-dioxa-7-aza-spiro[4.4]nonane-6-carboxylic acid methyl ester (42). A solution of the SEM ether **41a** (5 mg, 0.011 mmol) in anhydrous DMF (50 μL) was added to a stirred dispersion of sodium hydride (60% in mineral oil, 0.5 mg, 0.012 mmol) in anhydrous DMF (50 μL) at 0 °C. The suspension was stirred at 0 °C for 10 min and then iodomethane (30 μL,

0.22 mmol) was added in a single portion. The mixture was stirred at 0 °C for 15 min and then at room temperature for 1 h, before being diluted with ethyl acetate (0.5 mL) and water (0.5 mL). The aqueous phase was separated and the organic phase was extracted with water (3×0.5 mL). The organic extract was dried over $MgSO_4$ and evaporated in vacuo to leave the *N*-methylated pyrrolidinone (5 mg, 100%) as a colourless oil; $[\alpha]_D^{24}$ −1.3 (*c* 0.6, $CHCl_3$); ν_{max} ($CHCl_3$) 2929, 2356, 1738, 1689, 1058 cm^{-1}; δ_H (360 MHz, $CDCl_3$) 4.66 (1H, d, *J*=6.8, OCH_2O), 4.60 (1H, d, *J*=6.8, OCH_2O), 4.19 (1H, d, *J*=9.6, CH_2O), 4.13 (1H, d, *J*=9.6, CH_2O), 4.01 (1H, d, *J*=11.3, CH_2O), 3.84 (1H, d, *J*=9.1, CH_2O), 3.78 (3H, s, CO_2CH_3), 3.58 (2H, t, *J*=8.4, OCH_2CH_2Si), 2.86 (3H, s, NCH_3), 2.76 (1H, q, *J*=7.7, $CHCH_3$), 1.40 (3H, s, $C(CH_3)_2$), 1.33 (3H, s, $C(CH_3)_2$), 1.24 (3H, d, *J*=7.7, $CHCH_3$), 0.94 (2H, t, *J*=8.4, OCH_2CH_2Si), 0.04 (9H, s, $Si(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) 175.9 (*C*ONH), 168.7 (CO_2CH_3), 109.8 (CMe_2), 95.0 (OCH_2O), 86.0 (*C*(O)), 74.8 (quat. *C*), 65.9 (CH_2O), 65.6 (CH_2O), 64.8 (CH_2O), 52.4 (CO_2CH_3), 46.0 ($CHCH_3$), 27.3 (NCH_3), 27.2 (CCH_3), 25.6 (CCH_3), 18.1 (OCH_2CH_2Si), 11.3 ($CHCH_3$), −1.5 ($Si(CH_3)_3$; In a HMBC experiment (400 MHz, $CDCl_3$) δ_H 4.66 correlated to δ_C 65.9 and 65.6; δ_H 4.13 correlated to δ_C 109.8 and 46.0; δ_H 3.84 correlated to δ_C 86.0 and 74.8; δ_H 2.86 correlated to δ_C 175.9 and 74.8; *m/z* (ES) found 418.2275, 440.2101 ($M+H^+$, $C_{19}H_{36}NO_7Si$ requires 418.2261; M+Na, $C_{19}H_{35}NO_7SiNa$ requires 440.2080).

4.1.33. (5*S*,6*S*,9*R*)-6-Methoxymethyl-2,2,7,9-tetramethyl-8-oxo-1,3-dioxa-7-aza-spiro[4.4]nonane-6-carboxylic acid methyl ester (43b). A solution of the pivalate ester **41b** (4 mg, 0.011 mmol) in anhydrous DMF (50 μL) was added to a stirred dispersion of sodium hydride (60% in mineral oil, 1 mg, 0.017 mmol) in anhydrous DMF (50 μL) at 0 °C. The solution was stirred at 0 °C for 15 min before iodomethane (15 μL, 0.11 mmol) was added. The solution was stirred at 0 °C for 15 min and then at room temperature for 3 h. The solution was diluted with ethyl acetate (0.5 mL) and water (0.5 mL). The aqueous phase was separated and the organic phase was extracted with water (3×0.5 mL). The organic phase was dried over $MgSO_4$ and the solvent removed in vacuo. The residue was purified by flash column chromatography, on silica gel, eluting with diethyl ether to give the methyl ether (2 mg, 60%) as a colourless oil; δ_H (360 MHz, $CDCl_3$) 4.18 (1H, d, *J*=9.6, CH_2O), 4.12 (1H, d, *J*=9.6, CH_2O), 3.87 (1H, d, *J*=10.9, CH_2O), 3.78 (3H, s, CO_2CH_3), 3.66 (1H, d, *J*=10.9, CH_2O), 3.34 (3H, s, OCH_3), 2.84 (3H, s, NCH_3), 2.75 (1H, q, *J*=7.7, $CHCH_3$), 1.40 (3H, s, $C(CH_3)_2$), 1.34 (3H, s, $C(CH_3)_2$), 1.23 (3H, d, *J*=7.7, $CHCH_3$).

4.1.34. Oxazolidine (44). Paraformaldehyde (5 mg) was added to a stirred solution of the acetonide **39** (10 mg, 0.037 mmol), magnesium sulfate (5 mg, 0.042 mmol) and *para*-toluenesulfonic chloride (1 mg) in toluene (0.2 mL) at room temperature. The suspension was heated under reflux for 8 h and then allowed to cool before being diluted with a saturated solution of sodium bicarbonate (0.5 mL) and ethyl acetate (0.5 mL). The organic phase was separated and then the aqueous phase was extracted with ethyl acetate (3×0.5 mL). The combined organic extracts were dried over $MgSO_4$ and evaporated in vacuo. The residue was purified by flash column chromatography, on silica gel, eluting with diethyl ether and then ethyl acetate to give the oxazolidine (6 mg, 57%) as a colourless oil; $[\alpha]_D^{24}$ 16.5 (*c* 0.4, $CHCl_3$); ν_{max} ($CHCl_3$) 3425, 2955, 1704, 1383, 1059 cm^{-1}; δ_H (360 MHz, $CDCl_3$) 5.52 (1H, d, *J*=11.6, OCH_2N), 4.44–4.42 (1H, br, OCH_2N), 4.24 (1H, d, *J*=9.7, CH_2O), 4.19 (1H, d, *J*=9.7, CH_2O), 4.09–4.06 (2H, m, CH_2O), 3.80 (3H, s, CO_2CH_3), 2.75 (1H, q, *J*=7.8, $CHCH_3$), 1.40 (3H, s, $C(CH_3)_2$), 1.33 (3H, s, $C(CH_3)_2$), 1.25 (3H, d, *J*=7.7, $CHCH_3$); δ_C (100 MHz, $CDCl_3$) 178.1 (*C*ONH), 168.8 (CO_2CH_3), 109.9 (CMe_2), 85.8 (*C*(O)), 76.4 (quat. *C*), 65.8 (CH_2O), 65.2 (CH_2O), 61.8 (OCH_2N), 52.7 (CO_2CH_3), 46.6 ($CHCH_3$), 27.3 (CCH_3), 25.6 (CCH_3), 11.3 ($CHCH_3$); *m/z* (ES) found 286.1294 ($M+H^+$, $C_{13}H_{20}O_6N$ requires 286.1291).

4.1.35. (5*S*,6*S*,9*R*)-6-Hydroxymethyl-2,2,7,9-tetramethyl-8-oxo-1,3-dioxa-7-aza-spiro[4.4]nonane-6-carboxylic acid methyl ester (43a). Triethylsilane (4 μL, 0.033 mmol) was added to a stirred solution of the oxazolidine **44** (6.0 mg, 0.021 mmol) in trifluoroacetic acid (15 μL) and dichloromethane (0.15 mL). The solution was stirred at room temperature for 15 h before being diluted with a saturated aqueous solution of sodium bicarbonate (0.5 mL) and dichloromethane (0.5 mL). The organic phase was separated and the aqueous phase was extracted with dichloromethane (2×0.5 mL) and ethyl acetate (0.5 mL). The combined organic extracts were dried over $MgSO_4$ and the solvent evaporated in vacuo. The residue was purified by flash column chromatography, on silica gel, eluting with ethyl acetate to give the *N*-Me pyrrolidinone methanol (1.5 mg, 23%) as a colourless oil; δ_H (360 MHz, $CDCl_3$) 4.18–4.14 (3H, m, CH_2O), 4.07–4.04 (1H, m, CH_2O), 3.78 (3H, s, CO_2CH_3), 2.90 (3H, s, NCH_3), 2.84 (1H, q, *J*=7.1, $CHCH_3$), 1.38 (3H, s, $C(CH_3)_2$), 1.36 (3H, s, $C(CH_3)_2$), 1.23 (3H, d, *J*=7.1, $CHCH_3$); *m/z* (ES) found 288.1465 ($M+H^+$, $C_{13}H_{22}NO_6$ requires 288.1447).

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