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The total synthesis of pamamycin-607. Part 2: Synthesis of the C6–C18 domain

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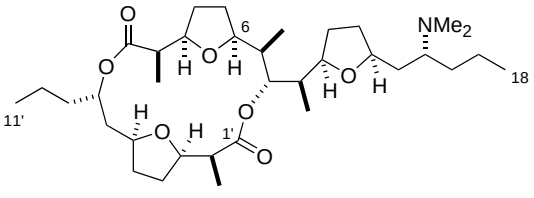
Abstract—Synthesis of the C6–C18 domain of pamamycin-607 was achieved in ten steps and 7% overall yield from commercially available D-norvaline. The key asymmetric transformations included a Paterson *anti* aldol addition, an *anti* selective reduction of the resultant β-hydroxy ketone and a cis selective Bartlett type ring closure.

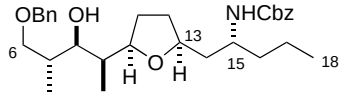
1. Introduction

Pamamycin-607 **1** (Scheme 1) is a member of a group of homologous naturally-occurring macrodiolides first isolated by Marumo from *Streptomyces alboniger* and *Streptomyces aurantiacus*.[1,2] Structurally, the interesting features include a 16-member macrodiolide and three *cis*-2,5-disubstituted tetrahydrofurans with adjacent methyl substituted stereogenic centres. Biologically, they show strong antibiotic activity against *Cochliobolus miyaneanus* and *Diaporthe citri*, but more importantly show potent activity against multiple antibiotic resistant strains of *Mycobacterium tuberculosis*.[3] Interestingly, this activity is due to their ability to inhibit adenine and uracil uptake.[4] Although structurally similar to the ionophore nonactin, pamamycin is incapable of transporting cations from aqueous to organic phases, but instead transports anions such as permanganate (MnO_4^-) and dichromate ($Cr_2O_7^{2-}$) from aqueous (pH ~ 5) to organic phases.[5–8] An interesting application of this was Grafe's demonstration of pamamycins capacity to transport drug molecules through the membranes of pathogenic bacteria.[9] In addition to antibiotic activity, the pamamycins also show autoregulatory activity by disrupting calcium ion accumulation and affecting aerial mycelium growth in *S. alboniger*.[8]

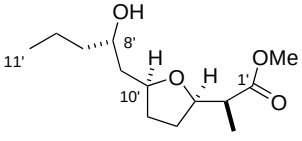
The aforementioned biological properties and complex stereochemistry make pamamycin-607 **1** an interesting



pamamycin-607 **1**



C6–C18 domain **3**



C1'–C11' domain **2**

Scheme 1. The C6–C18 (**3**) and C1′–C11′ **2** domains of pamamycin-607 (**1**).

Keywords: Tetrahydrofuran; Cyclisation; *anti* Aldol; Pamamycin; Stereoselective.
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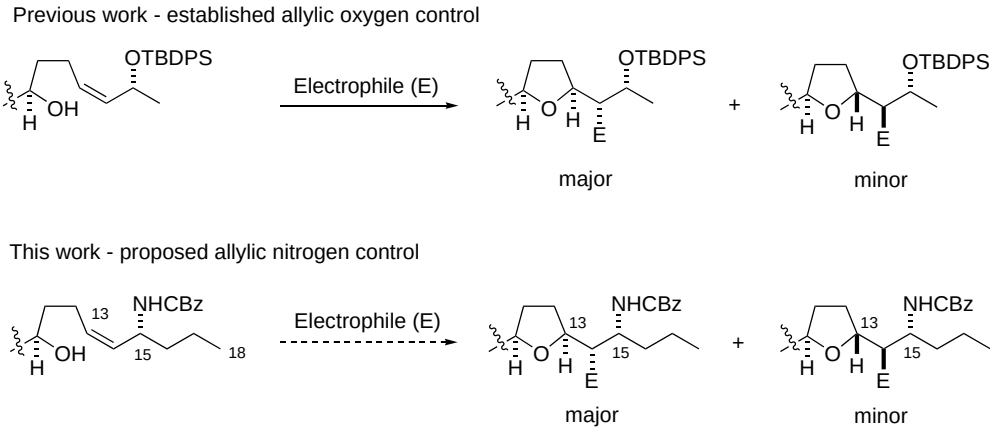


Scheme 2. Intramolecular electrophilic cyclisation of alkenes bearing a remote allylic heteroatom.

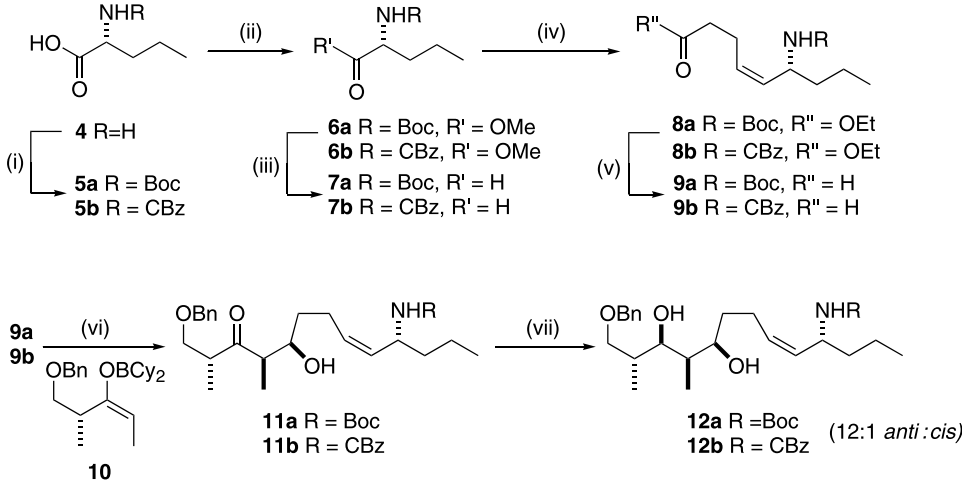
and challenging target for total synthesis, and indeed, so far four groups have reported total syntheses.[10–13] Towards that goal we previously reported a synthesis of the C1′–C11′ domain **2**.[14] Herein, we report our synthesis of the C6–C18 domain **3** of pamamycin-607 **1**.

Unlike other approaches, in our planned route to pamamycin-607 **1** the C15 allylic nitrogen was intended to be present throughout the synthesis, obviating the need for stereocontrolled introduction of nitrogen late in the synthesis. We envisaged applying an intramolecular electrophilic cyclisation reaction to form the key *cis* 2,5-disubstituted tetrahydrofuran moiety in a similar manner to that used to prepare the C1′–C11′ domain fragment **2** (Scheme 2).[14] It was anticipated that the C15 allylic nitrogen would influence the stereochemistry of the newly formed C13 centre, consistent with our previous work on related allylic oxygen systems.[15]

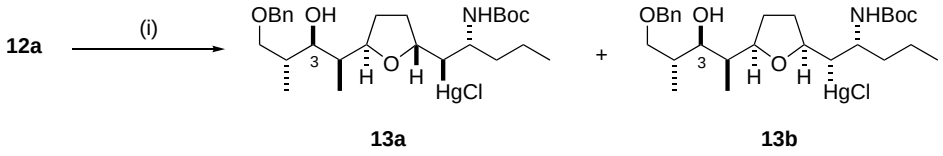
The diastereoselectivity of electrophilic cyclisations of alkenes bearing a remote protected allylic amine (Scheme 2) was not known at the beginning of this investigation and some preliminary results of our studies are included in this report.

2. Results and discussion

The synthesis began with the preparation of ring closure precursors **12a** and **12b** and was achieved in seven steps from commercially available D-norvaline **4** (Scheme 3). Treatment of D-norvaline **4** with benzylchloroformate/NaH gave CBz-D-norvaline **5b**, whilst the Boc analogue **5a** was obtained from a commercial supplier. Subsequent DIBAL-H reduction of the corresponding methyl esters **6a** and **6b** gave aldehydes **7a** and **7b** from which Wittig chain extension followed by DIBAL-H reduction afforded alkenals **9a** and **9b** in good yield and high *Z*:*E* selectivity (95:5, 96:4, respectively). Both aldehydes then underwent highly diastereoselective *anti* aldol addition with the (*E*)-enolate **10** of Paterson's chiral ketone **10a**[16] to afford diastereomerically pure aldols **11a** and **11b** after chromatography. The stereochemical assignment of **11a** and **11b** was consistent with literature precedent, and the $J_{2,3}$ coupling constants of 7.0, 7.1 Hz, respectively, are within the expected 7–9 Hz range for *anti* aldol adducts.[17] A final *anti*-selective reduction under Evans' conditions gave ring closure precursors **12a** and **12b** with excellent diastereoselectivity (both 12:1).[18,19]



Scheme 3. Synthesis of cyclisation precursors **12a** and **12b**. Reagents and conditions: (i) NaH, BnO_2CCl, DMF, 3 h, 100%; (ii) CH_2N_2, Et_2O, 0 °C, 1 h, **6a** 100%, **6b** 100%; (iii) DIBAL-H, toluene, −78 °C, 3 h; **7a** 78%, **7b** 97%; (iv) $BrPh_3P(CH_2)_3CO_2Et$, $NaN(TMS)_2$, THF, 0 °C, 1 h; **8a** 75%, **8b** 78%; (v) DIBAL-H, toluene, −78 °C, 3 h; **9a** 85%, **9b** 91%; (vi) **10**, ether, −78 °C, 2 h, −20 °C, o/n; **11a** 60%, **11b** 85%; (vii) $Me_4NBH(OAc)_3$, 1:1 AcOH/MeCN, −20 °C, 4 h, **12a** 68%, **12b** 78%.



Scheme 4. Cyclisation of diol **12a**. Reagents and conditions: (i) $Hg(OAc)_2$, MeCN, 0 °C, 3 h; 92%.

Investigation of electrophilic intramolecular cyclisations began with Boc diol **12a** (Scheme 4). Treatment with $Hg(OAc)_2$ at 0 °C in MeCN[15] gave a 10:1 mixture of *trans*-**13a** to *cis*-**13b**. Attempts to decrease or reverse this selectivity by decreasing reaction temperature were unsuccessful as reaction temperatures below 0 °C gave slow and impractical reaction rates. The use of the alternative electrophiles iodine and phenylselenium bromide was also unsuccessful and resulted in a complex mixture of inseparable products.

In order to establish if the C3 alcohol was playing any role in the observed trans selectivity, cyclisation of aldol adduct **11a** was carried out (Scheme 5). Treatment of **11a** with $Hg(OAc)_2$ in acetonitrile gave a 9:1 mixture of *trans* chloromercurial **14a** to *cis* chloromercurial **14b**.

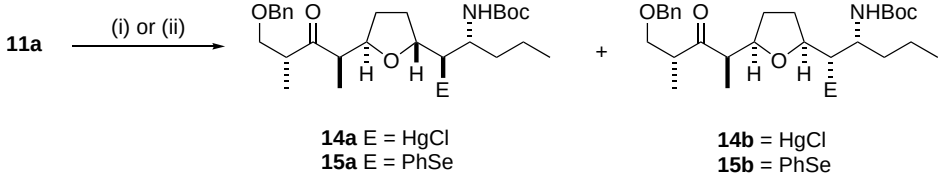
A similar result was obtained with PhSeBr where *trans*-tetrahydrofuran **15a** was favoured (5:1) over *cis*-tetrahydrofuran **15b** (Scheme 5). These results suggested that the C3 hydroxy was not an important factor in the observed trans selectivity.

Our previous work had shown the diastereoselectivity of this type of cyclisation was diminished for (*E*)-alkene substrates.[15] In an effort to reverse or suppress the trans-selectivity, (*E*)-alkene cyclisation precursor **19** was prepared by alkene isomerisation[20] of (*Z*)-ester **8a**. This was followed immediately by DIBAL reduction to give aldehyde **17**, which then underwent aldol addition to yield adduct **18**. A final *anti*-selective reduction afforded precursor **19** in good yield (Scheme 6).

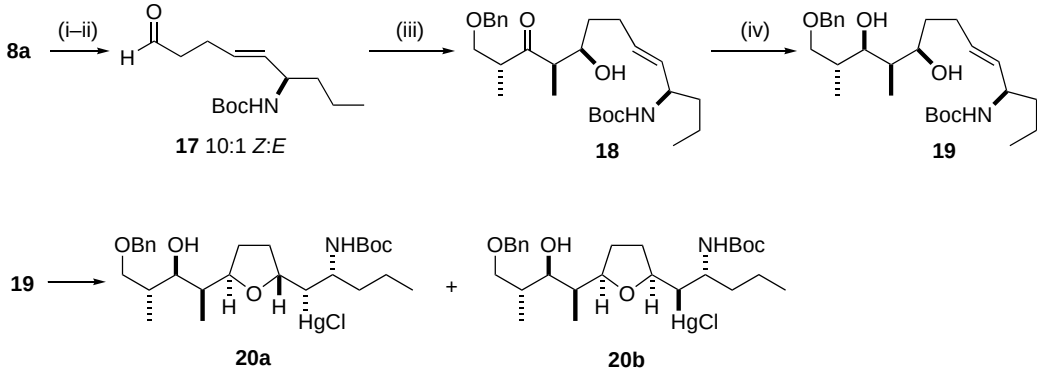
However, treatment of **19** with $Hg(OAc)_2$ in acetonitrile at 0 °C, again favoured the undesired *trans*-tetrahydrofuran **20a** over *cis*-**20b**, albeit with slightly improved (1:6) diastereoselectivity.

As forming the desired cis stereochemistry was proving difficult, we explored Bartlett's method for cis selective formation of 2,5-disubstituted tetrahydrofurans.[21] A similar approach was used by Kang, in their a total synthesis of pamamycin-607, which involved an iodine promoted cyclisation of a TES ether bearing a remote allylic oxygen substituent.[11] We first explored cyclisation of the TBS ether **23** derivative, which was easily prepared by treatment of diol **12b** with TBSOTf (Scheme 7).

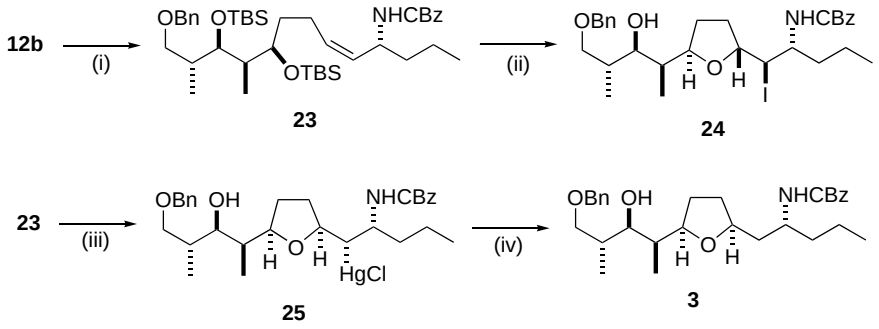
Subsequent iodocyclization of **23** proceeded in favour of *trans*-tetrahydrofuran **24**. This result may be due to cleavage of the TBS group being faster than the subsequent cyclization reaction. In an effort to reverse this result, the alternative electrophile $Hg(O_2CCF_3)_2$ was utilized with bis-TBS ether **23** in light of promising cis-selective oxymercurations of bis-TBS ethers reported by Walkup and co-workers.[22] Subsequent cyclisation of bis-TBS **23**



Scheme 5. Cyclisation of aldol adduct **11a**. Reagents and conditions: (i) $Hg(OAc)_2$, MeCN, 0 °C, 2 h; 73%; (ii) PhSeBr, DCM, −78 °C, 2 h, 52%.



Scheme 6. Synthesis and cyclisation of (*E*)-diol **19**. Reagents and conditions: (i) Ph_2S_2, benzene, hν, 2 days, (7:1 *E*/*Z*); (ii) DIBAL-H, toluene, −78 °C, 3 h, (10:1 *E*/*Z*); 51% over two steps; (iii) enolate **10**, ether, −78 °C, 2 h, −20 °C, o/n, 50%; (iv) $Me_4NBH(OAc)_3$, 1:1 AcOH/MeCN, −20 °C, 4 h, 92%; (v) $Hg(OAc)_2$, MeCN, 0 °C, 5 h, 60%.



Scheme 7. Synthesis and cyclisation of ether **23**. Reagents and conditions: (i) TBSOTf, 2,6-lutidine, THF, 0 °C, 4 h, 69%; (ii) I_2, $NaHCO_3$, MeCN, 0 °C, 3 h, 69%; (iii) $Hg(O_2CCF_3)_2$, DCM, −78 °C, 6 h, NaCl (satd), 51%; (iv) Bu_3SnH, AIBN, toluene, 60 °C, 3 h, 79%.

with $Hg(O_2CCF_3)_2$ in MeCN afforded *cis* tetrahydrofuran **25** in a 4:1 diastereoselectivity and moderate 48% yield. The *cis*-tetrahydrofuran stereochemistry was assigned by observation of an NOE between H2 and H5 of **25**. Removal of the chloromercurial group by treatment with tributylstannane and AIBN afforded the C6–C18 domain **3** in overall 7% yield from D-norvaline.

3. Conclusions

The combination of a Paterson aldol addition and *anti*-selective β-hydroxy ketone reduction has provided a very efficient and highly diastereoselective means for installing the four C7–C10 stereogenic centres of Pamamycin-607. A Bartlett type ring closure, using a $Hg(CO_2CF_3)_2$ electrophile reversed what appeared a highly trans-selective ring closure by providing a 4:1 cis selectivity. Further work is currently underway on the C1–C6 domain in our laboratories to complete our total synthesis of Pamamycin-607.

4. Experimental

4.1. General

Most chemicals were purchased from the Aldrich Chemical Company (Sydney, Australia) and were used as supplied. D-norvaline and Boc-D-norvaline were purchased from Novabiochem. Drying agents and inorganic salts were purchased from AJAX or BDH chemicals. Solvents were purified as follows. Anhydrous diethyl ether was distilled from sodium/benzophenone ketyl prior to use. Dichloromethane (DCM) was distilled from calcium hydride. Hexanes were distilled prior to use and refer to the fraction boiling between 40–60 °C. Silica gel used for chromatography was 40–63 μm (230–400 mesh) silica gel 60 (Merck No. 9385). Analytical thin-layer chromatography (TLC) was performed on Polygram Sil G/UV_{254} plastic sheets coated with silica gel containing UV_{254} fluorescent indicator and visualized under UV light and/or dipped in an ammonium molybdate/cerium sulphate solution. Proton NMR (^{1}H NMR) spectra were recorded at 300 MHz on a Varian Mercury spectrometer or Bruker AM 300 spectrometer and 400 MHz on a Bruker Avance DRX 400 spectrometer. Chemical shifts were recorded on the δ scale in parts per million (ppm). Unless otherwise stated, spectra were measured in deuterochloroform ($CDCl_3$) using the residual $CHCl_3$ (7.26 ppm) signal as an internal reference. Each resonance was reported according to the following convention: chemical shift (δ ppm) [multiplicity, coupling constant(s) (Hz), number of hydrogens. Multiplicities are designated as s=singlet, d=doublet, t=triplet, q=quartet, p=pentuplet and m=multiplet. Carbon NMR (^{13}C NMR) were recorded at 75 MHz on a Varian Mercury spectrometer or Bruker AM 300 spectrometer using deuterochloroform ($CDCl_3$) unless otherwise stated. The spectra were referenced using the solvent carbon signal ($CDCl_3$= 77.16 ppm). 2D NMR techniques such as homonuclear correlation spectroscopy (COSY), heteronuclear multiple quantum coherence (HMQC), heteronuclear multiple bond coherence (hmbc) and nuclear Overhauser effect spectroscopy (NOESY) were used to aid assignment of some NMR spectra. Mass spectrometry (ESI) was performed on a Micromass Platform QMS spectrometer. High-resolution mass spectra (HRMS) were recorded on a Bruker BioApex 47e FTMS using NaI for accurate mass calibration. M^+ refers to the molecular ion infrared spectra (IR) were recorded on a Perkin Elmer 1600 Series Fourier Transform spectrometer as neat solutions, chloroform ($CHCl_3$) solutions or as paraffin (Nujol) mulls of solids between NaCl plates. Melting points were recorded on a Kofler hot stage apparatus and are uncorrected.

4.1.1. (*R*)-2-Benzyloxycarbonylaminopentanoic acid (5b). To a solution of D-norvaline (5 g, 42.5 mmol) in THF (100 mL) at rt was added K_2CO_3 (29.4 g, 213 mmol) and benzylchloroformate (14.5 g, 12.1 mL, 85 mmol). The suspension was stirred o/n before being acidified to pH 1 with 2 M HCl. Ether (100 mL) was added and the organic phase separated from the aqueous phase, and the aqueous phase extracted with ether (3×20 mL). The combined organic extracts were then washed (satd $NaHCO_3$, brine), dried ($MgSO_4$) and the solvent removed under reduced pressure to yield the title compound **5b** as a colourless oil (10.7 g, 100%). $[\alpha]_D^{22}$ +19.5 (*c* 2.58, $CHCl_3$) lit.[23] (+14.1, *c* 1, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.94 (3H, t, *J*= 7.2 Hz, CH_2CH_3), 1.37–1.44 (2H, m, CH_2), 1.65–1.85 (2H, m, CH_2), 4.41 (1H, m, CHN), 5.12 (2H, br s, CH_2Ph), 5.36 (1H, d, *J*=8.2 Hz, NH), 7.26–7.39 (5H, m, ArH). ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.7, 18.6, 34.5, 53.7, 67.3, 128.2, 128.3, 128.6, 136.2, 156.2, 177.5. IR (neat) υ_{max} 3329, 3036, 2962, 2875, 1716 (broad), 1587, 1532, 1456, 1416, 1345, 1229, 1106, 1028, 910, 777, 735, 698 cm^{-1}. MS *m*/*z* 274.1 ($M+Na^+$). HRMS *m*/*z* calcd for $C_{13}H_{17}NO_4Na^+$= 274.1055. Found *m*/*z* 274.1049. Anal. Calcd for

$C_{13}H_{17}NO_4$: C, 62.1; H, 6.8; N, 5.6. Found: C, 62.2; H, 6.9; N, 5.3.

4.1.2. Methyl (*R*)-2-*tert*-butoxycarbonylaminopentanoate (6a). Diazomethane (generated from 5 g Diazald®/satd KOH) gas was passed through a solution of NBoc protected norvaline (5 g, 21.6 mmol) in ether (50 mL) at 0 °C. The solution immediately turned yellow and was allowed to stir at 0 °C for 1 h. Nitrogen was passed continuously through the solution until it became colourless, indicating dissipation of excess diazomethane. The ether was then removed under reduced pressure to give the title compound **6a** as a colourless oil (5.32 g, 100%). $[\alpha]_D^{22}$ −2.7 (*c* 1.68, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90 (3H, t, J=7.4 Hz, CH_2CH_3), 1.26–1.38 (2H, m, CH_2), 1.41 (9H, s, $C(CH_3)_3$), 1.46–1.80 (2H, m, CH_2), 3.70 (3H, s, CH_3 methyl ester), 4.26 (1H, m, C*H*N), 5.20 (1H, d, J=7.8 Hz, N*H*). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 19.0, 28.6, 35.2, 52.5, 53.5, 80.0, 155.5, 173.6. IR (neat) υ_{max} 3364, 2962, 2876, 1715, 1505, 1455, 1391, 1366, 1304, 1163, 1105, 1055, 1014, 919, 871, 780, 760 cm^{-1}. MS *m*/*z* 254.2 (M+Na$^+$). HRMS *m*/*z* calcd for $C_{11}H_{21}NO_4Na^+$=254.1368. Found: 254.1374. Anal. Calcd for $C_{11}H_{21}NO_4$: C, 57.2; H, 9.2; N, 6.1. Found: C, 57.3; H, 9.4; N, 6.2.

4.1.3. Methyl (*R*)-2-benzyloxycarbonylaminopentanoate (6b). Diazomethane (generated from 5 g Diazald®/satd KOH) gas was passed through a solution of NCBz protected norvaline **5b** (5 g, 18.9 mmol) in ether (50 mL) at 0 °C. The solution immediately turned yellow and was allowed to stir at 0 °C for 1 h. Nitrogen was then passed continuously through the solution until it became colourless, indicating dissipation of excess diazomethane. The ether was then removed under reduced pressure giving pure methyl ester **6b** as a colourless oil (5.28 g) in quantitative yield. $[\alpha]_D^{22}$ −2.8 (*c* 2.75, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.92 (3H, t, J=7.3 Hz, CH_2CH_3), 1.31–1.41 (2H, m, CH_2), 1.51–2.15 (2H, m, CH_2), 3.63 (3H, s, OCH_3), 4.37 (1H, m, C*H*N), 5.11 (2H, s, CH_2Bn CBz), 5.30 (1H, d, J=7.2 Hz, N*H*), 7.27–7.36 (5H, m, Ar*H*). ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.7, 18.6, 34.9, 52.3, 53.8, 67.1, 128.2, 128.6, 128.8, 136.4, 156.0, 173.2. IR (neat) υ_{max} 3342, 3065, 3033, 2880, 2874, 1725, 1714, 1538, 1455, 1380, 1304, 1216, 1170, 1105, 1061, 1027, 911, 778, 740, 698 cm^{-1}. MS *m*/*z* 288.1 (M+Na$^+$). HRMS *m*/*z* calcd for $C_{14}H_{19}NO_4Na^+$= 288.1212. Found: *m*/*z* 288.1216. Anal. Calcd for $C_{14}H_{19}NO_4$: C, 63.4; H, 7.2; N, 5.3. Found: C, 63.5; H, 7.2; N, 5.5.

4.1.4. (*R*)-2-*tert*-Butoxycarbonylaminopentanal (7a). To a solution of ester **6a** (5.32 g, 18.9 mmol) in toluene (150 mL) cooled to −78 °C was slowly added DIBAL-H (1 M in toluene, 54 mL, 54 mmol). Care was taken to ensure the reaction temperature did not exceed −70 °C during addition. The solution stirred for 2 h at −78 °C and was carefully quenched by addition of acetone (10 mL) and satd NH_4Cl (10 mL) whilst again being careful to maintain the reaction temperature below −70 °C. The solution was then warmed to rt, filtered, and the solvent removed under reduced pressure. The resultant crude oil was purified by flash chromatography (10% EtOAc/hexanes) yielding the title compound **7a** as a colourless oil (3.41 g, 78%). $[\alpha]_D^{22}$ −56.9 (*c* 1.875, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.94 (3H, t, J=7.2 Hz, CH_2CH_3), 1.32–1.60 (2H, m, CH_2), 1.43 (9H, s, $C(CH_3)_3$), 1.76–1.90 (2H, m, CH_2), 4.21 (1H, m, C*H*N), 5.06 (1H, br s, N*H*), 9.56 (1H, s, *H*C=O). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 18.9, 28.6, 31.6, 60.0, 80.2, 155.7, 200.1. IR (neat) υ_{max} 3350, 2964, 2875, 2815, 1720, 1698, 1518, 1458, 1392, 1387, 1252, 1169, 1063, 1017, 876, 782, 740 cm^{-1}. MS *m*/*z* 224.2 (M+Na$^+$). HRMS *m*/*z* calcd for $C_{10}H_{19}NO_3Na^+$=224.1263. Found: *m*/*z* 224.1253. Anal. Calcd for $C_{10}H_{19}NO_3$: C, 59.7; H, 9.5; N, 7.0%. Found: C, 59.8; H, 9.1; N, 7.2%.

4.1.5. (*R*)-2-Benzyloxycarbonylaminopentanal (7b). To a solution of ester **6b** (5.50 g, 19.7 mmol) in toluene (120 mL) cooled to −78 °C was slowly added DIBAL-H (1 M in toluene, 43.4 mL, 43.4 mmol). Care was taken to ensure reaction temperature did not exceed −70 °C during addition. The solution was stirred for 2 h at −78 °C and was carefully quenched by addition of acetone (10 mL) and satd NH_4Cl (10 mL) whilst again being careful to maintain a reaction temperature below −70 °C. The solution was then warmed to rt, filtered, and the solvent removed under reduced pressure. The resultant crude oil was purified by flash chromatography (10% EtOAc/hexanes) yielding the title compound **7b** as a colourless oil (4.49 g, 97%). $[\alpha]_D^{22}$ −40.7 (*c* 2.21, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.94 (3H, t, J=6.9 Hz, CH_2CH_3), 1.32–1.91 (4H, m, 2×C8H_2), 4.28 (1H, apparent q, J=7.2 Hz, C*H*N), 5.01 (2H, s, CH_2Ph), 5.50 (1H, d, J=6.6 Hz, N*H*), 7.26–7.35 (5H, m, Ar*H*), 9.54 (1H, s, *H*C=O). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 18.8, 31.4, 60.4, 67.4, 128.3, 128.4, 128.7, 136.4, 156.3, 199.6. IR (neat) υ_{max} 3332, 3066, 3033, 2961, 2934, 2874, 1712 (broad), 1521, 1456, 1405, 1381, 1339, 1256, 1179, 1065, 1028, 912, 843, 755, 698, 666 cm^{-1}. MS *m*/*z* 257.9 (M+Na$^+$). HRMS *m*/*z* calcd for $C_{13}H_{17}NO_3Na^+$= 258.1106. Found: *m*/*z* 258.1112. Anal. Calcd for $C_{13}H_{17}NO_3$: C, 66.4; H, 7.3; N, 6.0%. Found: C, 66.3; H, 7.3; N, 6.1%.

4.1.6. Ethyl (4*Z*)-(6*R*)-6-*tert*-butoxycarbonylaminonon-4-enoate (8a). To a stirred suspension of the triphenylphosphonium salt of ethyl 4-bromobutyrate (23.9 g, 52.2 mmol) in THF (150 mL) at 0 °C was added, dropwise, sodium bistrimethylsilylamide (1 M in THF, 52.2 mL, 52.2 mmol). Stirring continued at 0 °C for 1 h before aldehyde **7a** (3.00 g, 17.4 mmol) in THF (30 mL) was added dropwise over 10 min. The solution was then stirred at 0 °C for a further hour, after which time it was diluted with ether (100 mL) and poured into satd NH_4Cl (100 mL). The organic phase was separated from the aqueous phase and the aqueous phase extracted with ether (3×50 mL). The combined organic extracts were washed (brine), dried ($MgSO_4$), filtered, and the solvent removed under reduced pressure. The resulting crude yellow oil was subjected to flash chromatography (20% EtOAc/hexanes) to yield the title compound **8a** as a colourless oil (3.91 g, 75%). $[\alpha]_D^{22}$ −19.2 (*c* 1.34, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.87 (3H, t, J=6.9 Hz, CH_2CH_3), 1.21 (3H, t, J=7.2 Hz, CH_2CH_3 ethyl ester), 1.26–1.53 (4H, m, 2×CH_2), 1.39 (9H, s, $C(CH_3)_3$), 2.28–2.46 (4H, m, 2×CH_2), 4.06 (2H, q, J=7.2 Hz, CH_2CH_3 ethyl ester), 4.28 (1H, m, C*H*N), 4.45 (1H, br s, N*H*), 5.18 (1H, apparent t, J=9.9 Hz, *H*C=C), 5.40 (m, 1H, C=C*H*). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.3, 14.6, 19.3, 23.1, 23.5, 28.7, 34.5, 38.5, 60.6, 79.3, 129.8,

132.2, 155.2, 173.1. IR (neat) υ_{max} 3376, 2977, 2933, 2874, 1733, 1714, 1514, 1456, 1391, 1367, 1300, 1246, 1174, 1114, 1078, 1050, 699, 868, 773, 741 cm^{-1}. MS *m/z* 322.3 ($M+Na^+$). HRMS *m/z* calcd for $C_{16}H_{29}NO_4Na^+$ = 322.1994. Found: *m/z* 322.1981. Anal. Calcd for $C_{16}H_{29}NO_4$: C, 64.2; H, 9.8; N, 4.7%. Found: C, 63.7; H, 9.7; N, 4.8%.

4.1.7. Ethyl (4*Z*)-(6*R*)-6-benzyloxycarbonylaminonon-4-enoate (8b). To a stirred suspension of the triphenylphosphonium salt of ethyl 4-bromobutyrate (20.5 g, 44.7 mmol) in THF (150 mL) at 0 °C was added, dropwise, sodium bistrimethylsilylamide (1 M in THF, 44.7 mL, 44.7 mmol). Stirring continued at 0 °C for 1 h and after which aldehyde **7b** (3.50 g, 14.9 mmol) in THF (30 mL) was added dropwise over 10 min. The solution was then stirred at 0 °C for another hour, after which time it was diluted with ether (100 mL) and poured into satd NH_4Cl (100 mL). The organic phase was separated from the aqueous phase and the aqueous phase extracted with ether (3×50 mL). The combined organic extracts were washed (brine), dried ($MgSO_4$), filtered, and the solvent removed under reduced pressure. The resulting crude yellow oil was subjected to flash chromatography (20% EtOAc/hexanes) to yield the title compound **8b** as a colourless oil (3.80 g, 78%). $[\alpha]_D^{22}$ −33.0 (*c* 1.55, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 0.90 (3H, t, *J*=7.1 Hz, CH_2CH_3), 1.24 (3H, t, *J*=7.0 Hz, CH_2CH_3 ethyl ester), 1.28–1.40 (2H, m, CH_2), 1.46–1.58 (2H, m, CH_2), 2.28–2.54 (4H, m, 2×CH_2), 4.11 (2H, q, *J*=7.2 Hz, CH_2CH_3 ethyl ester), 4.39 (1H, m, C*H*N), 4.75 (1H, br s, N*H*), 5.07 (2H, br s, CH_2Ph), 5.21 (1H, m, *H*C=C), 5.47 (1H, m, C=C*H*), 7.26–7.39 (5H, m, Ar*H*). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.3, 14.6, 19.3, 23.5, 34.5, 36.2, 48.7, 60.7, 66.8, 128.2, 128.4, 128.7, 130.2, 131.7, 136.7, 155.7, 173.1. IR (neat) υ_{max} 3320, 2923, 2853, 1737, 1681, 1539, 1465, 1424, 1374, 1354, 1307, 1266, 1246, 1199, 1175. 1110, 1082, 1050, 1023, 1002, 723, 696 cm^{-1}. MS *m/z* 356.3 ($M+Na^+$). HRMS *m/z* calcd for $C_{19}H_{27}NO_4Na^+$ = 356.1838. Found: 356.1845. Anal. Calcd for $C_{19}H_{27}NO_4$: C, 68.5; H, 8.2; N, 4.2%. Found: C, 68.8; H, 8.2; N, 4.1%.

4.1.8. (4*Z*)-(6*R*)-6-*tert*-Butoxycarbonylaminonon-4-enal (9a). DIBAL-H (1 M in toluene, 21 mL, 21 mmol) was added slowly to a cooled solution of the ester **8a** (2.50 g, 8.35 mmol) in toluene (100 mL) whilst ensuring the reaction temperature did not exceed −70 °C. The solution stirred for 2 h at −78 °C and was carefully quenched by addition of acetone (10 mL) and satd NH_4Cl (10 mL) whilst again being careful to maintain a reaction temperature below −70 °C. The solution then warmed to rt, which induced precipitation of aluminium salts, was filtered and the solvent removed under reduced pressure giving a crude oil, which was subjected to flash chromatography (10% EtOAc/hexanes) to yield the title compound **9a** as a colourless oil (1.81 g, 85%). $[\alpha]_D^{22}$ −16.2 (*c* 1.86, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 0.80 (3H, t, *J*=7.2 Hz, CH_2CH_3), 1.20–1.45 (4H, m, 2×CH_2), 1.34 (9H, s, $C(CH_3)_3$), 2.25–2.48 (4H, m, 2×CH_2), 4.23 (1H, m, C*H*N), 4.48 (1H, d, *J*=7.9 Hz, N*H*), 5.12 (1H, ddq, *J*=10.5, 7.9, 1.3 Hz, *H*C=C), 5.30 (1H, dt, *J*=10.5, 6.8 Hz, C=C*H*), 9.65 (1H, d, *J*=1.4 Hz, *H*C=O). ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.8, 17.9, 19.5, 27.3, 37.0, 42.6, 46.6, 80.6, 128.1, 131.3, 154.1, 200.8. IR (neat) υ_{max} 3352, 2963, 2873, 1721, 1694, 1515, 1456, 1392, 1366, 1331, 1246, 1172, 1112, 1080, 1053, 1006, 900, 869, 772 cm^{-1}. MS *m/z* 278.2 ($M+Na^+$). HRMS *m/z* calcd for $C_{14}H_{25}NO_3Na^+$ = 278.1732. Found: *m/z* 278.1738. Anal. Calcd for $C_{14}H_{25}NO_3$: C, 65.9; H, 9.9; N, 5.5%. Found: C, 66.2; H, 10.1; N, 5.5%.

4.1.9. (4*Z*)-(6*R*)-6-Benzyloxycarbonylaminonon-4-enal (9b). DIBAL-H (1 M in toluene, 25 mL, 25 mmol) was added slowly to a cooled solution of the ester **8b** (3.80 g, 11.4 mmol) ensuring the reaction temperature did not exceed −70 °C. The solution stirred for 2 h at −78 °C and was then carefully quenched by addition of acetone (5 mL) and satd NH_4Cl (5 mL) whilst again being careful to maintain a reaction temperature below −70 °C. The solution was warmed to rt, which induced precipitation of aluminium salts, was filtered and the solvent removed under reduced pressure. The resultant crude oil, which was subjected to flash chromatography (10% EtOAc/hexanes) to yield the title compound **9b** as a colourless oil (3.01 g, 91%). $[\alpha]_D^{22}$ −25.6 (*c* 2.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 0.87 (3H, t, *J*=7.1 Hz, CH_2CH_3), 1.24–1.58 (4H, m, 2×CH_2), 2.32–2.60 (4H, m, 2×CH_2), 4.38 (1H, m, C*H*N), 4.65 (1H, m, N*H*), 5.06 (2H, br s, CH_2Ph), 5.21 (1H, apparent t, *J*=9.9 Hz, HC=C), 5.41 (1H, m, C=CH). ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.9, 18.0, 19.6, 36.9, 42.7, 47.4, 65.7, 127.2, 127.6, 127.9, 128.9, 130.9, 135.7, 154.7, 200.9. IR (neat) υ_{max} 3358, 1725, 1689 cm^{-1}. MS *m/z* 312.2 ($M+Na^+$). HRMS *m/z* calcd for $C_{17}H_{23}NO_3Na^+$ = 312.1276. Found: 312.1273. Anal. Calcd for $C_{17}H_{23}NO_3$: C, 70.6; H, 8.0; N, 4.8%. Found: C, 70.3; H, 8.2; N, 4.7%.

4.1.10. (4*E*)-(6*R*)-6-*tert*-Butoxycarbonylaminonon-4-enal (17). To a solution of ester **8a** (0.50 g, 1.67 mmol) in C_6D_6 was added Ph_2S_2 (72 mg, 0.33 mmol). The solution was then irradiated with UV light for 3 days. Daily monitoring of the reaction by ^1H NMR revealed after 3 days the isomerisation reaction had reached an equilibrium ratio of 7:1 *E*/*Z* alkenes. The solvent was then removed under reduced pressure and the crude oil passed through a short plug of silica gel (20% EtOAc/hexanes). The crude product was immediately dissolved in toluene (50 mL) and cooled to −78 °C. DIBAL (1 M in toluene, 2.5 mL, 2.5 mmol) was slowly added ensuring the reaction temperature did not exceed −70 °C. The solution stirred for 2 h at −78 °C and was then carefully quenched by addition of acetone (2 mL) and satd NH_4Cl (2 mL) whilist again being careful to maintain a reaction temperature below −70 °C. The solution then warmed to rt, which induced precipitation of aluminium salts, was then filtered and the solvent removed under reduced pressure giving a crude oil, which was subjected to flash chromatography (15% EtOAc/hexanes) to yield the title compound **17** (10:1 *E*/*Z*) as a colourless oil (217 mg, 51%). $[\alpha]_D^{22}$ +6.3 (*c* 0.95, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 0.85 (3H, t, *J*=7.2 Hz, CH_2CH_3), 1.17–1.42 (4H, m, 2×CH_2), 1.38 (9H, s, $C(CH_3)_3$), 2.28 (2H, dtd, *J*=6.4, 5.5, 1.1 Hz, CH_2), 2.46 (2H, dt, *J*=1.4, 5.5 Hz, CH_2), 3.96 (1H, m, C*H*N), 4.42 (1H, m, N*H*), 5.32 (1H, ddt, *J*=15.4, 6.2, 1.3 Hz, C=CH), 5.52 (1H, dtd, *J*=15.4, 6.3, 1.1 Hz, C=CH), 9.70 (1H, t, *J*=1.6 Hz, HC=O). ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.8, 19.0, 24.9, 37.7, 28.4, 43.2, 52.1, 79.2, 128.4, 132.5, 155.4, 201.8. IR (neat) υ_{max}

3351, 2960, 2932, 2874, 2723, 1715, 1698, 1520, 1456, 1391, 1366, 1248, 1173, 1079, 1053, 1009, 971, 871, 778 cm^{-1}. MS *m/z* 278.2 ($M+Na^+$). HRMS *m/z* calcd for $C_{14}H_{25}NO_3Na^+$ = 278.1732. Found: *m/z* 278.1728. Anal. Calcd for $C_{14}H_{25}NO_3$: C, 65.9; H, 9.9; N, 5.5%. Found: C, 65.8; H, 10.0; N, 5.6%.

4.1.11. (*R*)-1-Benzyloxy-2-methylpentan-3-one (10a). The known three-step procedure of Paterson and co-workers was followed and yielded the title compound **10a** as a colourless oil (8.78 g, 63% over three steps).[24] $[\alpha]_D^{22}$ −26.7 (*c* 8.0, $CHCl_3$) lit.[24] (−25.8, *c* 8.2, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 1.06 (3H, t, *J*=7.6 Hz, CH_2CH_3), 1.09 (3H, d, *J*=7.3 Hz, $CHCH_3$), 2.52 (2H, q, *J*=7.6 Hz, CH_2CH_3), 2.89 (1H, dqd, *J*=8.3, 7.3, 5.8 Hz, $CHCH_3$), 3.43 (1H, dd, *J*=9.4, 5.8 Hz, one of CH_2OBn), 3.62 (1H, dd, *J*=9.4, 8.3 Hz, one of CH_2OBn), 4.45 (1H, d, *J*=12.8 Hz, OCH_2Ph), 4.51 (1H, d, *J*=12.8 Hz, OCH_2Ph). ^{13}C NMR (75 MHz, $CDCl_3$) δ 7.6, 13.7, 35.6, 46.4, 72.5, 73.2, 127.8, 128.0, 128.8, 138.6, 214.1.

4.1.12. Benzyl (1*R*,2*Z*,6*R*,7*R*,9*R*)-10-benzyloxy-6-hydroxy-7, 9-dimethyl-8-oxo-1-propyl-dec-2-enyl)-carbamate (11b). The general *anti* aldol procedure of Paterson was applied.[16] To a stirred solution of dicyclohexylboronchloride (11.1 mL, 11.1 mmol, 1 M solution in hexanes) was added ether (20 mL). The solution was cooled to 0 °C and ketone **10a** (1.43 g, 6.93 mmol) and Et_3N (1.74 mL, 12.3 mmol) were added. The solution continued stirring for 2 h at 0 °C and was then cooled to −78 °C (dry ice/acetone bath). To this was added, dropwise, a solution of aldehyde **9b** (3.00 g, 10.4 mmol) in ether (10 mL). The solution continued stirring at −78 °C for 4 h before being transferred to a freezer (−20 °C) o/n. After removal from the freezer, the solution was diluted with methanol (30 mL) and pH 7 phosphate buffer (30 mL), and cooled to 0 °C. Hydrogen peroxide (12.0 mL, 30% aqueous) was then added dropwise and stirring continued for 3 h at rt. The solution was then diluted with DCM (50 mL) and the aqueous and organic phases separated. The aqueous phase was extracted with DCM (3×30 mL) and the combined organic extracts were washed (brine), dried ($MgSO_4$) and the solvent removed under reduced pressure to give a crude oil, which after flash chromatography (25% EtOAc/hexanes) yielded the title compound **11b** as a colourless oil (2.91 g, 85%). $[\alpha]_D^{22}$ −27.9 (*c* 2.11, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 0.91 (3H, t, *J*=7.1 Hz, CH_2CH_3), 1.03 (3H, d, *J*=7.0 Hz, $CHCH_3$), 1.08 (3H, d, *J*=7.1 Hz, $CHCH_3$), 1.20–1.41 (2H, m, CH_2), 1.50–1.61 (2H, m, CH_2), 1.69–1.93 (2H, m, CH_2), 2.11–2.28 (2H, m, CH_2), 2.30–2.48 (1H, m, one of CH_2), 2.73 (1H, apparent p, *J*=6.4 Hz, $CHCH_3$), 3.08 (1H, m, $CHCH_3$), 3.43 (1H, dd, *J*=5.0, 8.9 Hz, one of CH_2OBn), 3.60 (1H, m, CHOH), 3.68 (1H, dd, *J*=8.9, 8.7 Hz, one of CH_2OBn), 3.72 (1H, br s, OH), 4.41 (1H, m, CHN), 4.45 (1H, d, *J*=12.0 Hz, one of OCH_2Ph), 4.50 (1H, d, *J*=12.0 Hz, one of OCH_2Ph), 4.69 (1H, br s, NH), 5.08 (2H, s, CBz OCH_2Ph), 5.18 (1H, ddt, *J*=10.7, 7.9, 1.5 Hz, HC═C), 5.49 (dt, *J*=10.7, 7.9 Hz, 1H, C═CH), 7.23–7.38 (m, 10H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.3, 13.8, 14.0, 19.0, 24.2, 34.5, 35.6, 45.8, 48.5, 52.2, 66.7, 72.4, 73.1, 73.4, 127.7, 127.8, 128.2, 128.5, 128.6, 129.6, 130.7, 131.3, 158.1, 217.7. IR (neat) υ_{max} 3363, 3065, 3032, 2933, 2856, 1702, 1529, 1454, 1407, 1364, 1329, 1270, 1070, 1026, 970, 910, 844, 734, 698 cm^{-1}. MS *m/z* 518.3 ($M+Na^+$). HRMS *m/z* calcd for $C_{30}H_{41}NO_5Na^+$ = 518.2882. Found: *m/z* 518.2885. Anal. Calcd for $C_{30}H_{41}NO_5$: C, 72.7; H, 8.3; N, 2.8%. Found: C, 72.5; H, 8.4; N, 3.0%.

4.1.13. *tert*-Butyl (1*R*,2*Z*,6*R*,7*R*,9*R*)-(10-benzyloxy-6-hydroxy-7,9-dimethyl-8-oxo-1-propyl-dec-2-enyl)-carbamate (11a). The general procedure of Paterson was followed.[16] To a stirred solution of dicyclohexylboronchloride (11.6 mL, 11.6 mmol, 1 M solution in hexanes) was added ether (20 mL). The solution was cooled to 0 °C and ketone **10a** (1.49 g, 7.27 mmol) and Et_3N (1.81 mL, 12.8 mmol) were added. The solution continued stirring for 2 h at 0 °C and was then cooled to −78 °C (dry ice/acetone bath) after which a solution of aldehyde **9a** (2.32 g, 9.09 mmol) in ether (10 mL) was added dropwise. The solution continued stirring at −78 °C for 4 h before being transferred to a freezer (−20 °C) o/n. After removal from the freezer, the solution was diluted with methanol (30 mL) and pH 7 phosphate buffer (30 mL), and cooled to 0 °C. Hydrogen peroxide (10 mL, 30% aqueous) was then added dropwise and stirring continued for 3 h at rt. The solution was then diluted with DCM (50 mL) and the aqueous and organic phases separated. The aqueous phase was extracted with DCM (3×30 mL) and the combined organic extracts were washed (brine), dried ($MgSO_4$) and the solvent removed under reduced pressure to give a crude oil, which after flash chromatography (20% EtOAc/hexanes) yielded the title compound **11a** as a colourless oil (2.01 g, 60%). $[\alpha]_D^{22}$ −19.1 (*c* 2.65, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 0.91 (3H, t, *J*=7.1 Hz, CH_2CH_3), 1.04 (3H, d, *J*=7.0 Hz, $CHCH_3$), 1.08 (3H, d, *J*=7.1 Hz, $CHCH_3$), 1.11–1.39 (2H, m, CH_2), 1.39 (9H, s, $C(CH_3)_3$), 1.68–1.79 (2H, m, CH_2), 1.73–1.95 (2H, m, CH_2), 2.10–2.23 (1H, m, one of CH_2), 2.35–2.49 (1H, m, one of CH_2), 2.75 (1H, dq, *J*=7.0, 7.1 Hz, $CHCH_3$), 3.06 (1H, ddq, *J*=5.2, 8.9, 7.0 Hz, $CHCH_3$), 3.43 (1H, dd, *J*=5.2, 8.9 Hz, one of CH_2OBn), 3.62 (1H, m, CHOH), 3.67 (1H, dd, *J*=8.9, 8.9 Hz, one of CH_2OBn), 3.72 (1H, m, OH), 4.33 (1H, m, CHN), 4.42 (1H, m, NH), 4.44 (1H, d, *J*=12.1 Hz, one of OCH_2Ph), 4.50 (1H, d, *J*=12.1 Hz, one of OCH_2Ph), 5.16 (1H, ddt, *J*=10.6, 9.3, 1.3 Hz, HC═C), 5.47 (1H, dt, *J*=10.6, 8.0 Hz, C═CH), 7.25–7.37 (5H, m, ArH). ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.3, 12.6, 12.9, 18.7, 27.5, 29.1, 34.9, 37.9, 39.1, 40.4, 52.8, 72.5, 74.1, 75.7, 79.6, 125.5, 126.7, 126.8, 127.4, 127.8, 136.9, 154.5, 216.3. IR (neat) υ_{max} 3381, 2986, 2933, 2873, 1698, 1498, 1455, 1391, 1366, 1329, 1247, 1172, 1099, 1006, 755, 698, 666 cm^{-1}. MS *m/z* 484.4 ($M+Na^+$). HRMS *m/z* calcd for $C_{27}H_{43}NO_5Na^+$ = 484.3039. Found: *m/z* 484.3031. Anal. Calcd for $C_{27}H_{43}NO_5$: C, 70.3; H, 9.4; N, 3.0%. Found: C, 70.6; H, 9.2; N, 3.1%.

4.1.14. *tert*-Butyl (1*R*,2*E*,6*R*,7*R*,9*R*)-(10-benzyloxy-6-hydroxy-7,9-dimethyl-8-oxo-1-propyl-dec-2-enyl)-carbamate (18). The general procedure of Paterson was followed.[16] To a stirred solution of dicyclohexylboronchloride (1.25 mL, 1.25 mmol, 1 M solution in hexanes) was added ether (2 mL). The solution was cooled to 0 °C and ketone **10a** (161 mg, 0.78 mmol) and Et_3N (195 μl, 1.38 mmol) were added. The solution continued stirring for 2 h at 0 °C and was then cooled to −78 °C (dry ice/acetone bath) after which a solution of aldehyde **17** (250 mg, 0.98 mmol) in ether (1 mL) was added dropwise.

The solution continued stirring at −78 °C for 4 h before being transferred to a freezer (−20 °C) o/n. After removal from the freezer, the solution was diluted with methanol (3 mL) and pH 7 phosphate buffer (3 mL), and cooled to 0 °C. Hydrogen peroxide (1 mL, 30% aqueous) was then added dropwise and stirring continued for 3 h at rt. The solution was then diluted with DCM (5 mL) and the aqueous and organic phases separated. The aqueous phase was extracted with DCM (3×10 mL) and the combined organic extracts were washed (brine), dried ($MgSO_4$) and the solvent removed under reduced pressure to give a crude oil, which after flash chromatography (20% EtOAc/hexanes) yielded the title compound **18** as a colourless oil (180 mg, 50%). $[\alpha]_D^{21}$ +8.5 (*c* 1.76, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (3H, t, *J*=7.1 Hz, CH_2CH_3), 1.02 (3H, d, *J*=7.0 Hz, $CHCH_3$), 1.10 (3H, d, *J*=7.1 Hz, $CHCH_3$), 1.18–1.38 (4H, m, 2×CH_2), 1.43 (9H, s, $C(CH_3)_3$), 1.48–1.64m (2H, m, CH_2), 2.00–2.25 (2H, m, CH_2), 2.69 (1H, dq, *J*=7.1, 7.1 Hz, $CHCH_3$), 3.05 (1H, ddq, *J*=4.9, 8.9, 7.0 Hz, $CHCH_3$), 3.40 (1H, dd, *J*=4.9, 8.9 Hz, one of CH_2OBn), 3.68 (1H, dd, *J*=8.9, 8.9 Hz, one of CH_2OBn), 3.68 (1H, br s, O*H*), 3.96 (1H, m, C*H*N), 4.40–4.46 (1H, m, N*H*), 4.43 (1H, d, *J*=12.0 Hz, CH_2Ph), 4.48 (1H, d, *J*=12.0 Hz, CH_2Ph), 5.31 (1H, dd, *J*=15.3, 6.4 Hz, *H*C=C), 5.54 (1H, dt, *J*=15.3, 6.7 Hz, C=C*H*), 7.20–7.36 (5H, m, Ar*H*). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 14.1, 14.3, 19.4, 28.8, 29.0, 34.6, 38.2, 45.9, 52.4, 72.7, 73.2, 73.8, 79.5, 128.0, 128.1, 128.8, 130.7, 131.9, 137.2, 155.8, 218.2. IR (neat) υ_{max} 3444, 2978, 2935, 2875, 1706, 1498, 1456, 1391, 1367, 1244, 1168, 1076 cm^{-1}. MS *m*/*z* 484.3 ($M+Na^+$). HRMS *m*/*z* calcd for $C_{27}H_{43}NO_5Na^+$= 484.3039. Found: 484.3029. Anal. Calcd for $C_{27}H_{43}NO_5$: C, 70.3; H, 9.4; N, 3.0%. Found: C, 70.8; H, 9.3; N, 3.2%.

4.1.15. Benzyl (9*S*,8*S*,7*R*,6*R*,2*Z*,1*R*)-(10-benzyloxy-6,8-dihydroxy-7,9-dimethyl-1-propyl-dec-2-enyl)-carbamate (12b). The general procedure of Evans was followed.[18] To a solution of $Me_4NBH(OAc)_3$ (12.6 g, 28.3 mmol) in dry 1:1 acetonitrile/AcOH (10 mL) cooled to −15 °C was added a solution of aldol adduct **11b** (2.80 g, 5.65 mmol) in dry 1:1 acetonitrile/AcOH (10 mL). The solution was stirred for 4 h at −15 °C before being quenched by sodium potassium tartrate solution (0.5 M, 40 mL) and diluted with DCM (20 mL). The aqueous phase was separated from the organic phase and extracted with DCM (3×10 mL). The combined organics were then washed (satd $NaHCO_3$), dried ($Mg(SO_4)$) and the solvent removed under reduced pressure to give a crude oil, which upon purification by flash chromatography (40% EtOAc/hexanes) yielded the title compound **12b** as a colourless oil (2.21 g, 78%). $[\alpha]_D^{22}$ −59.9 (*c* 1.45, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.76 (3H, d, *J*=7.0 Hz, $CHCH_3$), 0.89 (3H, t, *J*=7.5 Hz, CH_2CH_3), 0.99 (3H, d, *J*=7.1 Hz, $CHCH_3$), 1.21–1.45 (4H, m, 2×CH_2), 1.45–1.91 (4H, m, CH_2), 2.05–2.43 (2H, m, CH_2), 3.49–3.65 (4H, m, 2×C*H*OH and CH_2OBn), 3.85 (1H, d, *J*=12.1 Hz, O*H*), 4.31–4.40 (1H, m, C*H*N), 4.45 (1H, m, O*H*), 4.52 (2H, br s, CH_2Ph), 4.75 (1H, br s, N*H*), 5.08 (2H, s, CH_2Ph CBz), 5.19 (1H, dd, *J*=9.3, 6.4 Hz, *H*C=C), 5.52 (1H, m, C=C*H*), 7.23–7.38 (m, 10H, Ar*H*). ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.9, 14.3, 14.7, 19.8, 27.4, 36.8, 36.3, 36.5, 37.9, 46.4, 65.9, 70.2, 71.9, 76.5, 77.1, 128.4, 128.5, 128.8, 130.8, 131.3, 137.7, 156.7. IR (neat) υ_{max} 3439, 2961, 2940, 2873, 1710, 1506, 1455, 1333, 1270, 1074, 1028, 975, 909, 733, 698, 648 cm^{-1}. MS *m*/*z* 520.4 ($M+Na^+$). HRMS *m*/*z* calcd for $C_{30}H_{43}NO_5Na^+$=520.3039. Found: 520.3033. Anal. Calcd for $C_{30}H_{43}NO_5$: C, 72.4; H, 8.7; N, 2.8%. Found: C, 72.5; H, 9.0; N, 2.7%.

4.1.16. *tert*-Butyl (9*S*,8*S*,7*R*,6*R*,2*E*,1*R*)-(10-benzyloxy-6,8-dihydroxy-7,9-dimethyl-1-propyl-dec-2-enyl)-carbamate (19). The general procedure of Evans was followed.[18] To a solution of $Me_4NBH(OAc)_3$ (0.5 g, 1.9 mmol) in dry 1:1 acetonitrile/AcOH (3.6 mL) cooled to −15 °C was added a solution of aldol adduct **18** (180 mg, 0.39 mmol) in dry 1:1 acetonitrile/AcOH (3.6 mL). The solution was stirred for 4 h at −15 °C before being quenched by sodium potassium tartrate solution (0.5 M, 5 mL) and diluted with DCM (5 mL). The aqueous phase was separated from the organic phase and extracted with DCM (3×5 mL). The combined organics were then washed (satd $NaHCO_3$), dried ($Mg(SO_4)$) and the solvent removed under reduced pressure to give a crude oil, which upon purification by flash chromatography (40% EtOAc/hexanes) yielded the title compound **19** as a colourless oil (166 mg, 92%). $[\alpha]_D^{21}$ +2.4 (*c* 1.66, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.72 (3H, d, *J*=6.9 Hz, $CHCH_3$), 0.88 (3H, t, *J*=7.4 Hz, CH_2CH_3), 0.98 (3H, d, *J*=7.0 Hz, $CHCH_3$), 1.18–1.40 (4H, m, 2×CH_2), 1.41 (9H, s, $C(CH_3)_3$), 1.53–1.78 (4H, m, 2×CH_2), 1.89–2.29 (2H, m, CH_2), 3.40–3.72 (5H, m, 2×C*H*OH, CH_2OBn and O*H*), 3.86 (1H, d, *J*=13.6 Hz, O*H*), 4.00 (1H, m, C*H*N), 4.37 (1H, br s, N*H*), 4.50 (2H, s, CH_2Ph), 5.34 (1H, dd, *J*=15.2, 5.1 Hz, *H*C=C), 5.56 (1H, dt, *J*=15.2, 6.5 Hz, C=C*H*), 7.18–7.34 (5H, m, Ar*H*). ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.5, 13.3, 14.2, 19.1, 28.5, 29.4, 35.5, 35.9, 36.5, 37.9, 52.3, 72.3, 72.7, 75.6, 76.5, 77.7, 127.5, 127.6, 128.3, 130.8, 131.3, 137.7, 156.7. IR (neat) υ_{max} 3450, 3349, 2931, 2873, 1694, 1504, 1455, 1392, 1366, 1333, 1248, 1172, 1098, 971, 870, 754, 698, 665 cm^{-1}. MS *m*/*z* 486.4 ($M+Na^+$). HRMS *m*/*z* calcd for $C_{27}H_{45}NO_5Na^+$486.3195. Found: 486.3194. Anal. Calcd for $C_{27}H_{45}NO_5$: C, 69.9; H, 9.8; N, 3.0%. Found: C, 70.3; H, 10.0; N, 3.2%.

4.1.17. *tert*-Butyl (9*S*,8*S*,7*R*,6*R*,2*Z*,1*R*)-(10-benzyloxy-6,8-dihydroxy-7,9-dimethyl-1-propyl-dec-2-enyl)-carbamate (12a). The general procedure of Evans was followed.[18] To a solution of $Me_4NBH(OAc)_3$ (1.34 g, 3.0 mmol) in dry 1:1 acetonitrile/AcOH (5 mL) cooled to −15 °C was added a solution of aldol adduct **11a** (0.5 g, 1.08 mmol) in dry 1:1 acetonitrile/AcOH (5 mL). The solution was stirred for 4 h at −15 °C before being quenched by sodium potassium tartrate solution (0.5 M, 10 mL) and diluted with DCM (10 mL). The aqueous phase was separated from the organic phase and extracted with DCM (3×5 mL). The combined organics were then washed (satd $NaHCO_3$), dried ($Mg(SO_4)$) and the solvent removed under reduced pressure to give a crude oil, which upon purification by flash chromatography (40% EtOAc/hexanes) yielded the title compound **12a** as a colourless oil (340 mg, 68%). $[\alpha]_D^{21}$ +1.3 (*c* 3.75, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.83 (3H, d, *J*=6.6 Hz, $CHCH_3$), 0.90 (3H, t, *J*=7.3 Hz, CH_2CH_3), 0.96 (3H, d, *J*=6.9 Hz, $CHCH_3$), 1.22–1.38 (4H, m, 2×CH_2), 1.41 (9H, s, $C(CH_3)_3$), 1.44–1.56 (4H, m, 2×CH_2), 2.19–2.38 (1H, m, one of CH_2), 2.45–2.65 (1H, m, one of CH_2), 3.43–3.61 (2H, m, C*H*OH and one of CH_2OBn), 3.61–3.73 (1H, m, one of CH_2OBn), 3.86 (1H, d, *J*=9.6 Hz, O*H*), 4.14 (1H, s, O*H*),

4.35 (1H, m, C*H*N), 4.50 (1H, m, C*H*OH), 4.51 (1H, d, J= 13.2 Hz, one of CH_2Ph), 4.55 (1H, d, J=13.2 Hz, one of CH_2Ph), 4.62 (1H, br s, N*H*), 5.16 (1H, apparent t, J= 10.2 Hz, *H*C=C), 5.34 (1H, dt, J=10.2 Hz, 4.5 Hz, C=C*H*), 7.22–7.39 (5H, m, Ar*H*). ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.7, 13.8, 14.1, 19.1, 23.8, 28.6, 35.6, 36.7, 38.1, 38.9, 48.1, 73.1, 73.5, 74.3, 75.1, 80.0, 127.7, 127.8, 128.6, 130.9, 132.2, 138.7, 155.8. IR (neat) υ_{max} 3430, 2962, 2932, 2873, 1688, 1520, 1455, 1366, 1247, 1170, 1086, 736, 697 cm^{-1}. MS *m/z* 486.5 (M+Na$^+$). HRMS *m/z* calcd for $C_{27}H_{45}NO_5Na^+$= 486.3195. Found: 486.3187. Anal. Calcd for $C_{27}H_{45}NO_5$: C, 69.9; H, 9.8; N, 3.0%. Found: C, 70.1; H, 9.7; N, 2.8%.

4.1.18. *tert*-Butyl (3′*S*,2′*S*,1′*S*,5″*R*,2″*R*,1α*R*,1*R*)-((1-{[5″-(4′-benzyloxy-2′-hydroxy-1′,3′-dimethyl-butyl)-tetrahydro-furan-2″-yl]-chloromercurio-methyl}-butyl)-carbamate (13a). To a stirred solution of diol **12a** (50 mg, 0.11 mmol) in acetonitrile (3 mL) at 5 °C was added mercury (II) acetate (120 mg, 0.38 mmol). The hetereogeneous mixture was stirred for 5 h at 5 °C. Brine (3 mL) was then added and stirring continued for another 1 h. The organic and aqueous phases were then separated and the aqueous phase extracted with DCM (3×2 mL). The combined organic extracts were dried ($MgSO_4$) and the solvent removed under reduced pressure to give a 10:1 mixture of chloromercurials *trans*-**13a** and *cis*-**13b**, which after purification by flash chromatography (25% EtOAc/hexanes) afforded the title compound **13a** (72 mg, 92%) as a colourless oil. $[\alpha]_D^{21}$ +24.5 (*c* 1.6, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.81 (3H, d, J=6.9 Hz, CHCH_3), 0.83 (3H, d, J=6.9 Hz, CHCH_3), 0.89 (3H, t, J=7.2 Hz, CH_2CH_3), 1.22–1.71 (7H, m, 2×CH_2, 2×C*H*CH_3 and one of CH_2), 1.34 (9H, s, C(CH_3)$_3$), 1.88–2.17 (3H, m, three of 2×CH_2), 2.99 (1H, apparent t, J=4.1 Hz, C*H*Hg), 3.39 (1H, br s, O*H*), 3.53 (1H, d, J=9.8 Hz, one of CH_2OBn), 3.59 (1H, d, J=9.8 Hz, one of CH_2OBn), 3.75 (1H, apparent dt, J=2.3, 9.2 Hz, C*H*OH), 3.87 (1H, m, C*H*N), 4.05 (1H, m, *H*COC), 4.25 (1H, dt, J=4.1, 5.0 Hz, *H*COC), 4.48 (1H, d, J=11.8 Hz, one of CH_2Ph), 4.55 (1H, d, J= 11.8 Hz, one of CH_2Ph), 4.89 (1H, d, J=8.4 Hz, N*H*), 7.22–7.34 (5H, m, Ar*H*). ^{13}C NMR (75 MHz, $CDCl_3$) δ 7.8, 12.6, 12.8, 18.7, 27.5, 29.6, 34.2, 34.9, 37.9, 39.1, 52.8, 66.1, 72.4, 74.1, 74.9, 77.0, 78.7, 79.5, 126.6, 126.7, 127.3, 136.9, 154.5. IR (neat) υ_{max} 3440, 3011, 2967, 2932, 2872, 1698, 1501, 1455, 1392, 1367, 1247, 1216, 1167, 1076, 1028, 997, 758, 698, 667 cm^{-1}. MS *m/z* 722.3 (M+Na$^+$). HRMS *m/z* calcd for $C_{27}H_{44}ClHgNO_5Na^+$=722.2512. Found: 722.2500. Anal. Calcd for $C_{27}H_{44}ClHgNO_5$: C, 46.4; H, 6.4, N, 2.0%. Found: C, 46.4; H, 6.5; N, 1.9%.

4.1.19. *tert*-Butyl (3′*R*,2′*R*,1′*R*,5″*R*,1α*R*,1*R*)-(1-{[5″-(4′-benzyloxy-1′,3′-dimethyl-2′-oxo-butyl)-tetrahydro-furan-2″-yl]-chloromercurio-methyl}-butyl)-carbamate (14a). To a stirred solution of aldol adduct **11a** (100 mg, 0.22 mmol) in acetonitrile (2 mL) at 5 °C was added mercury (II) acetate (138 mg, 0.43 mmol). The hetereogeneous mixture was stirred for 2 h at 5 °C. Brine (3 mL) was then added and stirring continued for another 1 h. The organic and aqueous phases were then separated and the aqueous phase extracted with DCM (3×2 mL). The combined organic extracts were dried ($MgSO_4$) and the solvent removed under reduced pressure to give a 9:1 mixture of chloromercurials *trans*-**14a** and *cis*-**14a**, which after purification flash chromatography (25% EtOAc/hexanes) afforded the title compound **14a** (110 mg, 73%) as a semi-crystalline colourless oil. $[\alpha]_D^{21}$ +6.7 (*c* 3.02, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90 (3H, t, J= 7.2 Hz, CH_2CH_3), 0.97 (3H, d, J=6.9 Hz, CHCH_3), 1.09 (3H, d, J=7.0 Hz, CHCH_3), 1.21–61 (6H, m, 3×CH_2), 2.01–2.21 (2H, m, CH_2), 2.72–2.82 (1H, m, C*H*CH$_3$), 2.96–3.07 (2H, m, C*H*CH$_3$ and C*H*Hg), 3.47 (1H, dd, J=5.5, 9.0 Hz, one of CH_2OBn), 3.63 (1H, dd, J=7.7, 9.0 Hz, one of CH_2OBn), 3.84–3.89 (1H, m, C*H*N), 4.10–4.21 (1H, m, *H*COC), 4.29–4.35 (1H, m, *H*COC), 4.36 (1H, d, J= 12.0 Hz, one of CH_2Ph), 4.50 (1H, d, J=12.0 Hz, one of CH_2Ph), 4.79 (1H, apparent d, J=7.1 Hz, N*H*), 7.21–7.38 (m, 5H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.8, 13.6, 14.1, 19.9, 30.6, 35.4, 39.0, 47.1, 51.5, 54.1, 67.2, 72.7, 73.5, 79.0, 80.1, 81.0, 127.8, 127.9, 128.6, 138.4, 155.6, 215.1. IR (neat) υ_{max} 3362, 2927, 1709, 1678, 1521, 1455, 1367, 1295, 1251, 1169, 1114, 1050, 994, 911, 730, 695 cm^{-1}. MS *m/z* 720.2 (M+Na$^+$). HRMS *m/z* calcd for $C_{27}H_{42}ClHgNO_5Na^+$=720.2355. Found: 720.2341. Anal. Calcd for $C_{27}H_{42}ClHgNO_5$: C, 46.6; H, 6.1; N, 2.0%. Found: C, 46.3; H, 6.3; N, 2.2%.

4.1.20. *tert*-Butyl (3′*R*,1′*R*,5″*R*,2″*R*,1α*R*,1*R*)-(1-{[5″-(4′-benzyloxy-1′,3′-dimethyl-2′-oxo-butyl)-tetrahydro-furan-2″-yl]-phenylselanyl-methyl}-butyl)-carbamate (15a). To a stirred solution of PhSeBr (102 mg, 0.43 mmol) in DCM (2 mL) at −78 °C was added a solution of ketone **11a** (100 mg, 0.22 mmol) in DCM (2 mL). The homogeneous mixture stirred for 4 h at −78 °C before satd $NaHCO_3$ (4 mL) was added. The organic and aqueous phases were then separated and the aqueous phase extracted with DCM (3×3 mL). The combined organic extracts were dried ($MgSO_4$) and the solvent removed under reduced pressure to give a 5:1 mixture of selenylphenyls *trans*-**15a** and *cis*-**15b**, which after purification by flash chromatography (20% EtOAc/hexanes) afforded pure **15a** (70 mg, 52%) as pale yellow oil. $[\alpha]_D^{21}$ −23.8 (*c* 1.04, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (3H, t, J=7.3 Hz, CH_2CH_3), 0.98 (3H, d, J=6.0 Hz, CHCH_3), 1.09 (3H, d, J=6.9 Hz, CHCH_3), 1.21–1.65 (4H, m, 2×CH_2), 2.00–2.14 (4H, m, 2×CH_2), 2.77–2.84 (1H, m, C*H*CH$_3$), 3.01–3.18 (1H, m, C*H*CH$_3$), 3.50 (1H, dd, J=5.7, 9.1 Hz), 3.52 (1H, m, C*H*Se), 3.64 (1H, dd, J=7.4, 9.1 Hz, one of CH_2OBn), 3.87 (1H, m, C*H*N), 4.18 (1H, apparent dd, J= 4.9, 9.4 Hz, *H*COC), 4.22–4.29 (1H, m, *H*COC), 4.46 (1H, d, J=12.0 Hz, one of CH_2Ph), 4.51 (1H, d, J=12.0 Hz, one of CH_2Ph), 5.00 (1H, d, J=9.3 Hz, N*H*), 7.17–7.38 (8H, m, Ar*H*), 7.52–7.58 (2H, m, Ar*H*). ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.6, 12.9, 13.9, 19.5, 28.4, 30.8, 31.7, 34.6, 46.6, 51.6, 55.0, 59.3, 72.6, 73.2, 78.9, 79.6, 82.7, 126.9, 127.5, 127.7, 128.3, 129.0, 130.1, 133.6, 138.2, 156.1, 215.4. IR (neat) υ_{max} 3378, 2966, 2945, 1706, 1687, 1518, 1455, 1365, 1247, 1171, 1076, 1023, 738, 696 cm^{-1}. MS. *m/z* 640.2 (M+Na$^+$). HRMS *m/z* calcd for $C_{33}H_{47}NO_5SeNa^+$=640.2517. Found: 640.2504. Anal. Calcd for $C_{33}H_{47}NO_5Se$: C, 64.3; H, 7.7, N, 2.3%. Found: C, 64.6; H, 7.8; N, 2.5%.

4.1.21. *tert*-Butyl (3′*S*,2′*S*,1′*S*,5″*R*,2″*R*,1α*S*,1*R*)-(1-{[5″-(4′-benzyloxy-2′-hydroxy-1′,3′-dimethyl-butyl)-tetrahydro-furan-2″-yl]-chloromercurio-methyl}-butyl)-carbamate (20a). To a stirred solution of (*E*)-diol **19** (166 mg, 0.36 mmol) in acetonitrile (4 mL) at 0 °C was

added mercury (II) acetate (215 mg, 0.72 mmol). The hetereogeneous mixture was stirred for 5 h at 5 °C before warming to rt and stirring o/n. Brine (4 mL) was then added and stirring continued for another 1 h. The organic and aqueous phases were then separated and the aqueous phase extracted with DCM (3×3 mL). The combined organic extracts were dried ($MgSO_4$) and the solvent removed under reduced pressure to give a 4:1 mixture of chloromercurials *trans*-**20a** and *cis*-**20b**, which after purification of the mixutre by flash chromatography (25% EtOAc/hexanes) gave pure **20a** (150 mg, 60%) as a colourless oil. $[\alpha]_D^{21}$ +15.1 (*c* 2.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.79 (3H, d, J=5.5 Hz, CHCH_3), 0.81 (3H, d, J=6.8 Hz, CHCH_3), 0.88 (3H, t, J=7.3 Hz, CH_2CH_3), 1.11–1.65 (7H, m, 2×CH_2, 2×CHCH$_3$ and one of CH_2), 1.85–1.98 (1H, m, one of CH_2), 2.02–2.10 (1H, m, one of CH_2), 2.15–2.29 (1H, m, one of CH_2), 2.85 (1H, apparent t, J=4.5 Hz, CHHg), 3.41 (1H, br s, OH), 3.53 (1H, d, J=11.5 Hz, one of CH_2OBn), 3.72 (1H, dt, J=11.5, 2.3 Hz, one of CH_2OBn), 3.81–3.99 (1H, m, CHOH), 3.99–4.05 (1H, m, HCOC), 4.18–4.29 (1H, m, HCOC), 4.47 (1H, d, J=11.9 Hz, one of CH_2Ph), 4.52 (1H, d, J=11.9 Hz, one of CH_2Ph), 4.80 (1H, d, J=8.2 Hz, NH), 7.21–7.33 (5H, m, ArH). ^{13}C NMR (75 MHz, $CDCl_3$) δ 7.8, 12.6, 12.9, 18.5, 27.6, 29.8, 34.6, 35.1, 37.7, 39.0, 51.9, 64.2, 72.4, 73.9, 74.7, 77.7, 80.8, 79.8, 126.6, 126.8, 127.4, 137.0, 154.4. IR (neat) υ_{max} 3448, 3011, 2966, 2932, 2873, 1686, 1499, 1455, 1392, 1367, 1248, 1216, 1166, 1092, 1047, 1092, 1047, 951, 872, 759, 699, 668 cm^{-1}. MS *m*/*z* 722.2 (M+Na$^+$). HRMS *m*/*z* calcd for $C_{27}H_{44}ClHgNO_5Na^+$=722.2512. Found: 722.2508. Anal. Calcd for $C_{27}H_{44}ClHgNO_5$: C, 46.4; H, 6.4; N, 2.0%. Found: C, 46.3; H, 6.6; N, 2.1%.

4.1.22. Benzyl (9*S*,8*R*,7*R*,6*R*,2*Z*,1*R*) [10-benzyloxy-6,8-bis-(*tert*-butyl-dimethyl-silanyloxy)-7,9-dimethyl-1-propyl-dec-2-enyl]-carbamate (23). To a solution of diol **12b** (100 mg, 0.20 mmol) in THF (3 mL) was added 2,6-lutidine (155 µl, 1.34 mmol) and TBSOTf (230 µl, 1.0 mmol). The solution stirred for 4 h at rt before being quenched by satd NH_4Cl (5 mL). The solution was diluted with DCM (5 mL) and the organic and aqueous phases separated. The aqueous phase was extracted with DCM (3×3 mL) and the combined organic extracts were washed (brine), dried ($MgSO_4$) and the solvent removed under reduced pressure to give a crude oil, which after purification by flash chromatography (25% EtOAc/hexanes) yielded the title compound **23** (101 mg, 69%) as a colourless oil. $[\alpha]_D^{22}$ −4.2 (*c* 1.7, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.01 (12H, s, 2×Si(CH_3)$_2$), 0.85–0.90 (24H, m, 2×SiC(CH_3)$_3$, CHCH_3 and CH_2CH_3), 0.96 (3H, d, J=6.9 Hz, CHCH_3), 1.24–1.60 (6H, m, 3×CH_2), 1.91–2.31 (3H, m, CH_2 and CHCH$_3$), 3.25 (1H, dd, J=8.1, 9.2 Hz, one of CH_2OBn), 3.53 (1H, dd, J=5.2, 9.2 Hz, CH_2OBn), 3.59–3.65 (2H, m, 2×CHOTBS), 4.36 (1H, m, CHN), 4.44 (1H, d, J=12.0 Hz, CH_2Ph), 4.49 (1H, d, J=12.0 Hz, CH_2Ph), 4.55 (1H, br s, NH), 5.05 (2H, br s, CH_2Ph CBz), 5.15 (1H, apparent dt, J=10.7, 1.6 Hz, HC=C), 5.43 (1H, dt, J=10.7, 7.0 Hz, C=CH), 7.25–7.33 (10H, m, ArH). ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.2, −5.2, −4.7, −4.6, 9.6, 12.9, 13.7, 17.1, 17.4, 24.9, 25.1, 31.2, 37.2, 38.5, 40.5, 47.7, 65.5, 71.6, 72.1, 73.1, 73.9, 126.4, 126.5, 126.6, 126.9, 127.3, 127.5, 129.3, 131.4, 135.7, 137.8, 156.1. IR (neat) υ_{max} 3334, 2956, 2930, 2857, 1712, 1498, 1463, 1361, 1339, 1255, 1076, 1005, 835, 772, 734, 694 cm^{-1}. MS *m*/*z* 748.5 (M+Na$^+$). HRMS *m*/*z* calcd for $C_{42}H_{71}NO_5Si_2Na^+$= 748.4768. Found: 748.4765. Anal. Calcd for $C_{42}H_{71}NO_5Si_2$: C, 69.5; H, 9.9; N, 1.9%. Found: C, 69.4; H, 10.0; N, 1.8%.

4.1.23. Benzyl (3′*S*,2′*S*,1′*S*,5″*R*,2″*R*,1α*R*,1*R*)-(1-{[5″-(4′-benzyloxy-2′-hydroxy-1′,3′-dimethyl-butyl)-tetrahydro-furan-2″-yl]-iodo-methyl}-butyl)-carbamate (24). An adaptation of the general iodocyclisation procedure of Bartlett was followed.[21] To a solution of TBS ether **23** (48 mg, 0.07 mmol) in acetonitrile (2 mL) at −10 °C was added a solution of iodine (34 mg, 0.14 mmol) in acetonitrile (2 mL). The solution was stirred for 1 h at −10 °C before being quenched by pH 7 phosphate buffer (5 mL) and satd sodium sulphite solution (2 mL). The solution was then diluted with DCM (5 mL) and the organic and aqueous phases separated. The aqueous phase was extracted with DCM (3×3 mL) and the combined organic extracts were washed (brine), dried ($MgSO_4$) and the solvent removed under reduced pressure to give a 5:1 crude mixture of *cis*/*trans* tetrahydrofurans, which after purification by flash chromatography (25% EtOAc/hexanes) yielded the title compound **24** (101 mg, 69%) as a colourless oil. $[\alpha]_D^{22}$ −4.1 (*c* 0.6, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.84 (1H, d, J=6.9 Hz, CHCH_3), 0.85 (1H, d, J=6.9 Hz, CHCH_3), 0.93 (3H, t, J=7.3 Hz, CH_2CH_3), 1.30–1.55 (4H, m, 2×CH_2), 1.61–1.72 (2H, m, CH_2), 1.78–2.18 (4H, m, 2×CHCH$_3$ and CH_2), 3.19 (1H, d, J=3.0 Hz, OH), 3.51 (1H, d, J=5.8 Hz, one of CH_2OBn), 3.57–3.71 (1H, m, one of CH_2OBn), 3.57–3.61 (1H, m, CHN), 3.61–3.69 (1H, m, HCOC), 3.72–3.78 (1H, dt, J=9.2, 3.0 Hz, CHOH), 4.10–4.17 (1H, m, HCOC), 4.39 (1H, apparent t, J=3.5 Hz, CHI), 4.42 (1H, d, J=11.8 Hz, one of CH_2Ph), 4.48 (1H, d, J=11.8 Hz, one of CH_2Ph), 5.10 (2H, s, CH_2Ph CBz), 5.48 (1H, d, J=9.0 Hz, NH), 7.24–7.36 (10H, m, ArH). ^{13}C NMR (75 MHz, $CDCl_3$) δ 9.1, 14.0, 14.1, 19.6, 30.6, 36.2, 36.6, 40.3, 48.6, 56.1, 66.8, 73.5, 75.4, 75.6, 78.5, 82.4, 127.7, 128.0, 128.1, 128.5, 128.6, 128.7, 136.3, 137.5, 155.8. IR (neat) υ_{max} 3450, 3155, 2965, 1794, 1717, 1508, 1466, 1382, 1217, 1095, 912, 731, 651 cm^{-1}. MS *m*/*z* 646.2 (M+Na$^+$). HRMS *m*/*z* calcd for $C_{30}H_{42}INO_5Na^+$= 646.2005. Found: 646.1990. Anal. Calcd for $C_{30}H_{42}INO_5$: C, 57.8; H, 6.8; N, 2.3%. Found: C, 57.5; H, 6.7; N, 2.1%.

4.1.24. Benzyl (3′*S*,2′*S*,1′*S*,5″*R*,2″*S*,1α*S*,1*R*)-(1-{[5″-(4′-benzyloxy-2′-hydroxy-1′,3′-dimethyl-butyl)-tetrahydro-furan-2″-yl]-chloromercurio-methyl}-butyl)-carbamate (25). An adaptation of the cyclisation procedure of Walkup was used.[22] To a solution of bis-TBS ether **23** (100 mg, 0.14 mmol) in acetonitrile (4 mL) at 0 °C was added $Hg(O_2CCF_3)_2$ (71 mg, 0.17 mmol). The solution was warmed to rt and stirred for a further 2 h before being quenched by addition of satd NH_4Cl (4 mL) and brine (4 mL). The solution was then stirred for another 1 h before being diluted with DCM (4 mL) and the organic and aqueous phases separated. The aqueous phase was extracted with DCM (3×3 mL) and the combined organic extracts were washed (brine), dried ($MgSO_4$) and the solvent removed under reduced pressure to give a 4:1 mixture of *cis*/*trans* chloromercurials, which after purification by flash chromatography (20% EtOAc/hexanes) yielded the title compound **25** (52 mg, 51%) as a colourless oil. $[\alpha]_D^{21}$ +11.9 (*c* 2.3, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.79 (3H, d,

J=6.9 Hz, CHCH_3), 0.82 (3H, d, J=6.9 Hz, CHCH_3), 0.87 (3H, t, J=7.0 Hz, CH_2CH_3), 1.26–1.71 (6H, m, 3×CH_2), 1.85–2.21 (4H, m, 2×C*H*CH$_3$ and CH_2), 2.81 (1H, dd, J= 4.5, 6.1 Hz, C*H*Hg), 3.53–3.57 (2H, m, one of CH_2OBn and O*H*), 3.68 (1H, m, one of CH_2OBn), 3.79–3.86 (2H, m, C*H*OH and *H*COC), 3.92–4.01 (1H, m, C*H*N), 4.11–4.17 (1H, m, *H*COC), 4.20 (1H, d, J=11.7 Hz, CH_2Ph), 4.52 (1H, d, J=11.7 Hz, CH_2Ph), 4.97 (1H, d, J=9.6 Hz, N*H*), 7.22–7.32 (10H, m, Ar*H*). ^{13}C NMR (75 MHz, $CDCl_3$) δ 9.1, 13.5, 14.0, 19.2, 31.1, 31.7, 34.2, 36.1, 40.2, 41.5, 54.2, 67.5, 73.1, 77.1, 75.5, 78.6, 80.6, 81.3, 127.8, 127.8, 127.9, 127.9, 128.2, 128.3, 128.6, 128.7, 136.1, 137.2, 156.2. IR (neat) υ_{max} 3374, 2969, 2933, 1708, 1509, 1455, 1366, 1249, 1169, 1098, 912, 734, 698 cm^{-1}. MS m/z 756.3 (M+Na$^+$). HRMS m/z calcd for $C_{30}H_{42}ClHgNO_5Na^+$=756.2355. Found: 756.2361. Anal. Calcd for $C_{30}H_{42}ClHgNO_5$: C, 49.2; H, 5.8; N, 1.9%. Found: C, 49.1; H, 5.9; N, 2.0%.

4.1.25. Benzyl (3′*S*,2′*S*,1′*S*,5″*R*,2″*S*,1*R*)-{1-[5″-(4′-benzyloxy-2′-hydroxy-1′,3′-dimethyl-butyl)-tetrahydro-furan-2″-ylmethyl]-butyl}-carbamate (3). To a solution of chloromercurial **25** (50 mg, 0.07 mmol) in toluene at rt (2 mL) was added Bu_3SnH (45 μl, 0.17 mmol) and AIBN (7 μmol). Precipitation of metallic mercury occurred almost immediately and stirring continued o/n after which CCl_4 (2 mL) was added and stirring continued for a further 2 h. The solution was then diluted with 25% DCM/hexanes (10 mL) and washed with 5% KF solution (3×5 mL). The organic phase was washed (brine), dried ($MgSO_4$) and the solvent removed under reduced pressure giving a crude grey oil, which after purification by flash chromatography (20% EtOAc/hexanes) yielded the title compound **3** as a colourless oil (27 mg, 79%). $[\alpha]_D^{21}$ −5.1 (c 1.12, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.84 (3H, d, J=7.1 Hz, CHCH_3), 0.88 (3H, d, J=6.9 Hz, CHCH_3), 0.96 (3H, t, J=10.7 Hz, CH_2CH_3), 1.21–1.64 (6H, m, 3×CH_2), 1.88–2.21 (6H, m, 2×CH_2 and 2×C*H*CH$_3$), 3.40 (1H, br s, O*H*), 3.51 (1H, dd, J=6.6, 11.2 Hz, one of CH_2OBn), 3.62 (1H, dd, J=7.2, 11.2 Hz, one of CH_2OBn), 3.78–3.85 (2H, m, C*H*OH and *H*COC), 3.89 (1H, m, C*H*N), 4.15 (1H, m, *H*COC), 4.31 (1H, d, J=10.8 Hz, CH_2Ph), 4.58 (1H, d, J=10.8 Hz, CH_2Ph), 4.78 (1H, d, J=8.2 Hz, N*H*), 7.21–7.38 (10H, m, Ar*H*). ^{13}C NMR (75 MHz, $CDCl_3$) δ 8.5, 12.3, 12.9, 18.4, 28.4, 30.7, 32.7, 36.4, 40.8, 49.2, 65.9, 72.8, 73.5, 75.6, 77.0, 78.3, 80.2, 80.7, 127.7, 127.8, 127.8, 127.9, 127.9, 128.1, 128.5, 128.9, 136.4, 136.8, 156.7. IR (neat) υ_{max} 3482, 2946, 2917, 2853, 1460, 1348, 1245, 1235, 1145, 1095, 1045, 791, 773 cm^{-1}. MS m/z 520.3 (M+Na$^+$). HRMS m/z calcd for $C_{30}H_{43}NO_5Na^+$=520.3039. Found: 520.3046. Anal. Calcd for $C_{30}H_{43}NO_5$: C, 72.4; H, 8.7; N, 2.8. Found: C, 72.7; H, 8.6; N, 2.8.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2006.01.005. NOESY spectra of **13a**, **14a**, **15a**, **20a**, **24** and **25** for assignment of *cis*/*trans* tetrahydrofuran stereochemistry. This information is available free of charge via the internet at http://pubs.acs.org.

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