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Stereoselective synthesis of hydroxylated 3-aminoazepanes using a multi-bond forming, three-step tandem process†

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A multi-bond forming, three-step tandem process involving a palladium(II)-catalysed Overman rearrangement and a ring closing metathesis reaction has been utilised for the efficient synthesis of a 2,3,6,7-tetrahydro-3-amidoazepine. Substrate directed epoxidation or dihydroxylation of this synthetic intermediate has allowed the diastereoselective synthesis of hydroxylated 3-aminoazepanes including the *syn*-diastereomer of the balanol core. Asymmetric synthesis of the 2,3,6,7-tetrahydro-3-amidoazepine motif was also achieved using a chiral palladium(II)-catalyst during the Overman rearrangement.

Introduction

The azepane ring system is an important structural motif found in many pharmaceutically active compounds and natural products.[1] Amino-substituted azepane rings in particular, make up the core of several important natural products and medicinal agents such as (–)-balanol (**1**), a metabolite of the fungi *Verticillium balanoides* and a potent inhibitor of human protein kinase C (Fig.1).[2] Other important aminoazepanes include azelastine (**2**),[3] a selective histamine antagonist and zilpaterol (**3**), a β-adrenergic agonist used as a feed additive for cattle.[4] Due to the interest in using amino-substituted azepanes as pharmacologically active building blocks and as conformationally constrained peptidomimetics,[5] there has been much focus on developing methods for their synthesis.[6,7] For example, Braga and co-workers prepared a trihydroxylated aminoazepane from D-glucitol via an aziridine ring opening reaction,[7c] while Würdemann and Christoffers utilised an intramolecular 1,3-dipolar cycloaddition between a nitrone and an allylic amine to generate a *cis*-5-aminoazepan-3-ol.[7e] Most synthetic methods developed for the preparation of aminoazepanes have focused on the generation of the *trans*-3-amino-4-hydroxyazepane core of balanol (**1**)[8] and include samarium iodide mediated cyclisation of oxime ethers[8b,8c] as well as ring closing metathesis (RCM) of amino-substituted dienes to form the azepane ring system.[8d,8e, 8h,8i]

While many of these synthetic methods allow the efficient stereoselective synthesis of amino-substituted azepane rings, they all rely on traditional single-step transformations that require their own set of reagents, solvents and conditions as well as the yield reducing isolation and purification of each intermediate. Cascade, domino or tandem processes overcome many limitations of single-step transformations and allow the formation of multiple bonds and molecular complexity, all in a single pot operation.[9] We now report the efficient preparation of a 2,3,6,7-tetrahydro-3-amidoazepine using a multi-bond forming, three-step tandem process. We also demonstrate how this flexible synthetic intermediate can be subjected to substrate directed oxidation reactions for the diastereoselective preparation of hydroxylated 3-aminoazepanes including the *syn*-diastereomer of the balanol core.

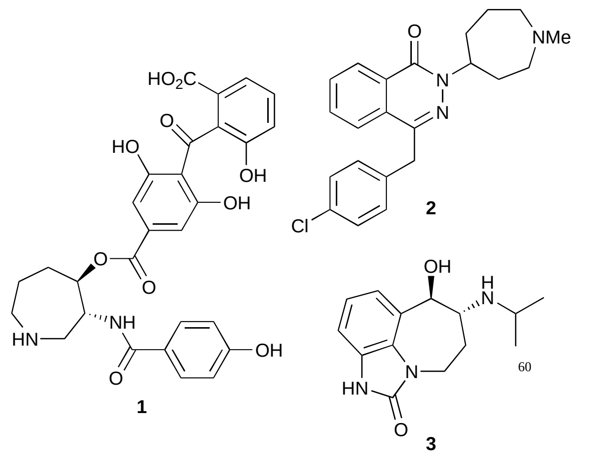
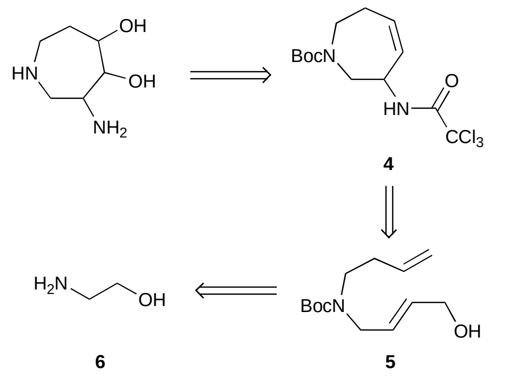


Fig. 1 Structures of aminoazepane containing compounds.

Results and discussion

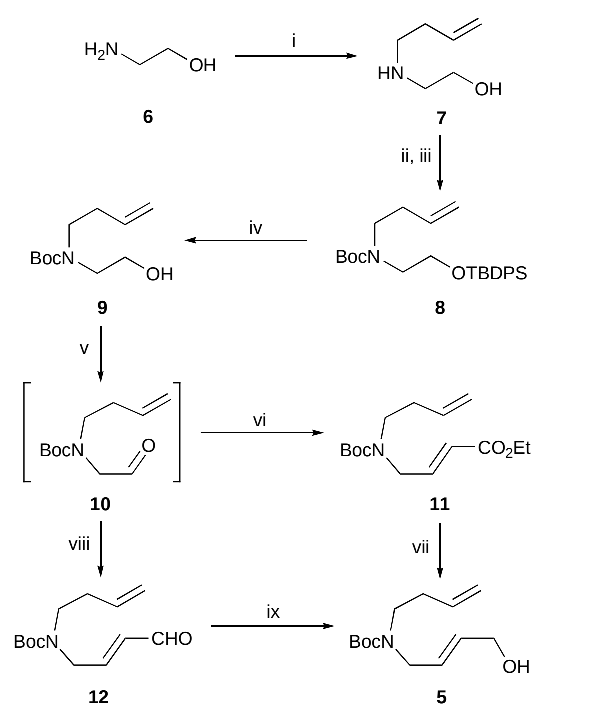
Our synthesis of hydroxylated 3-aminoazepanes is outlined in Scheme 1. It was proposed that allylic alcohol **5** could be easily generated using inexpensive, readily available 2-aminoethanol (**6**). A three-step tandem process involving a palladium(II)-catalysed Overman rearrangement and a RCM reaction was then envisaged for the preparation of 2,3,6,7-tetrahydro-3-amidoazepine **4**. Subsequent stereoselective oxidation of the alkene using the trichloroacetamide substituent as a directing group would lead to the hydroxylated 3-aminoazepanes.



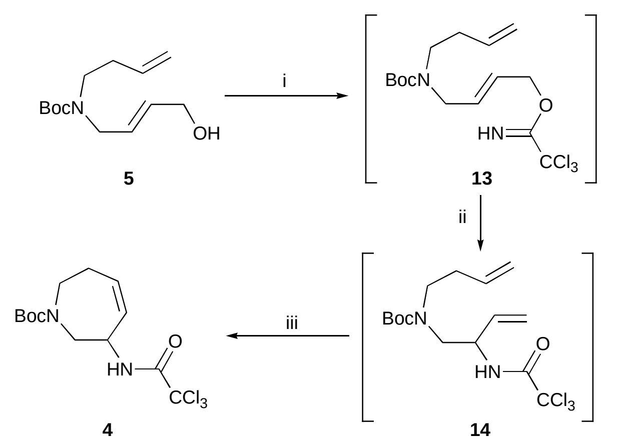
Scheme 1 Proposed route to hydroxylated 3-aminoazepanes.

Initially, a synthetic route was developed for the efficient preparation of allylic alcohol **5** (Scheme 2), the substrate for the tandem process. 2-Aminoethanol (**6**) was coupled with 4-bromo-1-butene in the presence of sodium iodide to give **7** in quantitative yield. Silyl protection of the primary alcohol then allowed Boc-protection of the secondary amine. Removal of the silyl protecting group under standard conditions gave alcohol **9** which was then subjected to a one-pot Swern oxidation and Horner-Wadsworth-Emmons reaction under Masamune-Roush conditions.[10,11] This gave exclusively *E*-α,β-unsaturated ester **11** in 94% yield over the two steps. DIBAL-H reduction of **11** was attempted but gave *E*-allylic alcohol **5** in only 37% yield along with a complex mixture of compounds. It is well-known that α,β-unsaturated esters containing adjacent heteroatoms can undergo competing 1,4-addition rather than 1,2-reduction due to complexation of the metal hydride with the heteroatom.[12] This can be overcome using the Moriwake modification that involves addition of a Lewis acid to protect the heteroatom.[12] However, attempted reduction of **11** using DIBAL-H in the presence of boron trifluoride diethyl etherate gave **11** in only a slightly improved yield of 41%. Due to the issues associated with reduction of **11**, a more efficient route to *E*-allylic alcohol **5** was achieved via α,β-unsaturated aldehyde **12**. Primary alcohol **9** was subject to a Swern oxidation which gave aldehyde **10** in 94% yield. Wittig reaction of **10** with (triphenylphosphoranylidene)acetaldehyde followed by reduction of the aldehyde moiety with sodium borohydride reduction gave *E*-allylic alcohol **5** in 88% yield. This seven-step synthesis was particularly amenable to scale-up (~5 g) giving allylic alcohol **5** in 53% overall yield from 2-aminoethanol (**6**).

Allylic alcohol **5** was then subjected to the three-step tandem process for the preparation of 2,3,6,7-tetrahydro-3-amidoazepine **4** (Scheme 3).[13] Allylic alcohol **5** was converted to allylic trichloroacetimidate **13** under standard conditions, followed by rearrangement with bis(acetonitrile)palladium(II) chloride.[14,15] As part of the one-pot tandem process, **14** was initially treated with Grubbs 1st generation catalyst.[16] However, this required a RCM reaction time of 96 hours giving 2,3,6,7-tetrahydro-3-amidoazepine **4** in 49% from **5**. The RCM step of the tandem process was improved substantially using Grubbs 2nd generation catalyst,[17] which gave 2,3,6,7-tetrahydro-3-amidoazepine **4** after only 12 hours and in 79% overall yield.



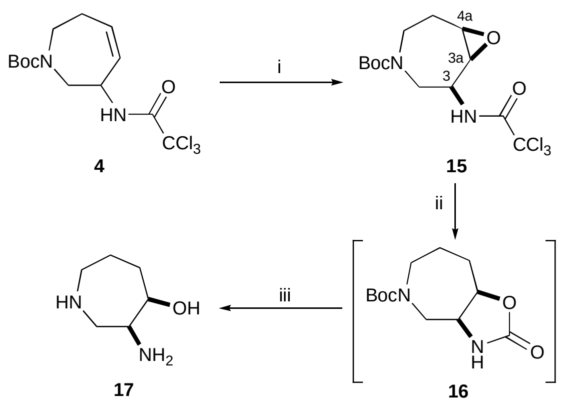
Scheme 2 *Reagents and conditions*: (i) 4-bromo-1-butene, NaI, MeOH, Δ, 100%; (ii) TBDPSCl, imidazole, THF, rt, 86%; (iii) Boc_2O, Et_3N, DMAP, CH_2Cl_2, rt, 100%; (iv) TBAF, THF, 0 ºC, 100%; (v) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, –78 °C, 94%; (vi) $(EtO)_2P(O)CH_2CO_2Et$, DBU, LiCl, MeCN, rt, 94% from **9**; (vii) DIBAL-H, BF_3OEt_2, CH_2Cl_2, –78 °C, 41%; (viii) $Ph_3P{=}CHCHO$, toluene, 80 °C, 75%; (ix) $NaBH_4$, MeOH, 0 °C, 88%.



Scheme 3 *Reagents and conditions*: (i) Cl_3CCN, DBU (25 mol%), CH_2Cl_2, rt; (ii) $PdCl_2(MeCN)_2$ (10 mol%), CH_2Cl_2, rt; (iii) Grubbs II (10 mol%), Δ, 79% over three steps.

Having developed the tandem process for the facile synthesis of 2,3,6,7-tetrahydro-3-amidoazepine **4**, the programme of research then focused on the diasteroselective oxidation of this synthetic intermediate using the allylic trichloroacetamide moiety as a directing group. Initial studies focused on the preparation of the *syn*-diastereomer of the balanol core. Directed epoxidation of

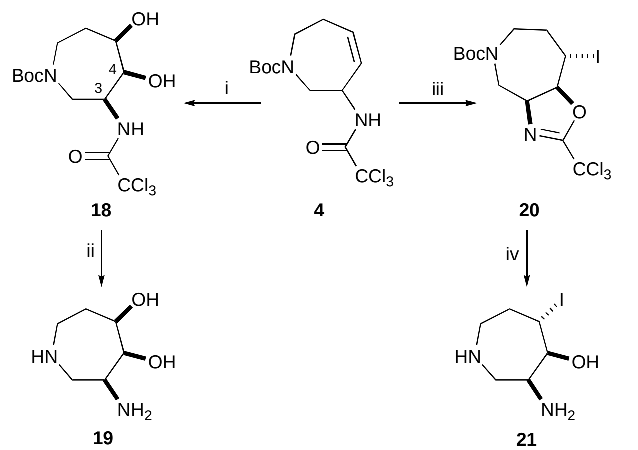
4 using *m*-CPBA[18,19] gave **15** as a single diastereomer in 58% yield (Scheme 4). The relative stereochemistry was confirmed by difference NOE experiments which clearly showed the *syn*-relationship of the 3-, 3a- and 4a-hydrogen atoms.[20] Regioselective reductive ring opening of the epoxide was performed using $LiAlH_4$ which gave bicyclic oxazolidinone **16**. Without purification, removal of the Boc-protecting group and hydrolysis of the oxazolidinone ring was achieved under acid mediated conditions to give the *syn*-diastereomer of the balanol core, (3*S**,4*R**)-3-aminoazepin-4-ol (**17**) in 61% yield from **15**.



Scheme 4 *Reagents and conditions*: (i) *m*-CPBA, CH_2Cl_2, rt, 58%; (ii) $LiAlH_4$, THF, Δ; (iii) 6N HCl, MeOH, rt, 61% over two steps.

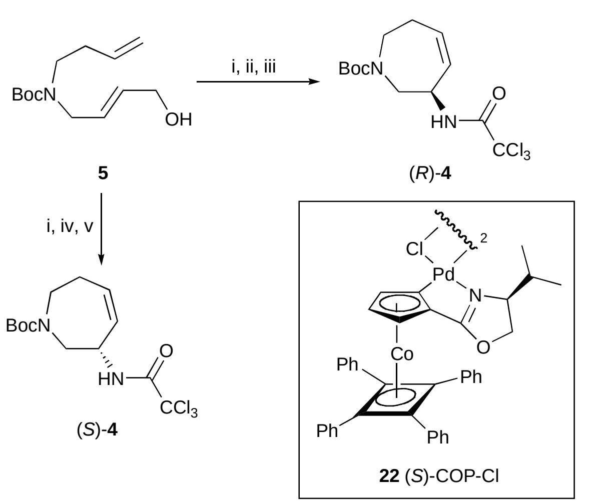
In an effort to generate azepines with a higher level of substitution, conditions for the directed dihydroxylation of **4** were next investigated. Donohoe and co-workers have shown that highly stereoselective substrate directed dihydroxylation of cyclic allylic trichloroacetamides can be achieved using a reagent generated from osmium tetroxide and *N*,*N*,*N'*,*N'*-tetramethylethylenediamine (TMEDA).[21] This method proved particularly effective for the selective dihydroxylation of cycloheptenes.[21c] Using 2,3,6,7-tetrahydro-3-amidoazepine **4** as a substrate for this reaction gave *syn*-diol **18** in 81% yield and as a single diastereomer (Scheme 5). Difference NOE experiments confirmed the relative stereochemistry of **18** with clear correlation between the hydrogen atoms at C-3 and C-4.[20] Removal of the protecting groups under standard conditions gave (3*S**,4*S**,5*R**)-3-aminoazepane-4,5-diol (**19**) in 78% yield.

Biologically active compounds incorporating an iodine atom are important both as synthetic intermediates in organic chemistry and as molecular tracers for single photon emission computed tomography (SPECT) imaging.[22] It was proposed that 2,3,6,7-tetrahydro-3-amidoazepine **4** could be used in a substrate directed iodination to access an iodinated stereoisomer of **17**. Reaction of **4** with *N*-iodosuccinimide gave 4,5-dihydro-1,3-oxazole **20** in 78% yield (Scheme 5).[23] As is well precedented for this reaction, generation of the iodonium intermediate takes place *anti* to the trichloroacetamide group.[14e,23] This is followed by *syn*-formation of the 4,5-dihydro-1,3-oxazole ring, ultimately yielding **20** as a single diastereomer.[20] Acid mediated hydrolysis of the 4,5-dihydro-1,3-oxazole ring and concurrent removal of the Boc-group was achieved under mild conditions to give (3*S**,4*S**,5*S**)-3-amino-5-iodoazepane-4-ol (**21**) in 77% yield.



Scheme 5 *Reagents and conditions*: (i) OsO_4, TMEDA, CH_2Cl_2, –78 °C, 81%; (ii) 2M NaOH, MeOH, 40 °C then 2M HCl, 78%; (iii) *N*-iodosuccinimide, $CHCl_3$, rt, 78%; (iv) 0.5M HCl, MeOH, rt, 77%.

While the oxidation of 2,3,6,7-tetrahydro-3-amidoazepine **4** using these reactions leads to the highly efficient preparation of functionalised aminoazepanes as single diastereomers, these compounds are racemic due to the formation of **4** as a racemate during the three-step tandem process. We therefore wanted to demonstrate the enantioselective synthesis of **4**. The groups of Richards and Overman have developed a series of chiral palladium(II) complexes such as (*S*)-COP-Cl **22** which have been shown to effect the rearrangement of allylic trichloroacetimidates in excellent yields and with high enantioselectivity.[24] Using commercially available (*S*)-COP-Cl **22** (5 mol%) to catalyse the Overman rearrangement during the three-step tandem process gave (*R*)-2,3,6,7-tetrahydro-3-amidoazepine **4** in 92% yield and in 92% enantiomeric excess (Scheme 6).[25] In a similar fashion, use of (*R*)-COP-Cl gave the (*S*)-enantiomer in 84% yield and in 92% ee. Having demonstrated the asymmetric synthesis of **4**, these products now have the potential to be used for the enantioselective preparation of highly functionalised aminoazepanes.



Scheme 6 *Reagents and conditions*: (i) Cl_3CCN, DBU, CH_2Cl_2, rt; (ii) (*S*)-COP-Cl (5 mol%), CH_2Cl_2, rt; (iii) Grubbs II (10 mol%), Δ, 92% over three steps; (iv) (*R*)-COP-Cl (5 mol%), CH_2Cl_2, rt; (v) Grubbs II (10 mol%), Δ, 84% over three steps.

Conclusions

In summary, a highly efficient, multi-bond forming, three-step tandem process has been developed for the racemic and asymmetric synthesis of a 2,3,6,7-tetrahydro-3-amidoazepine. The utility of this compound as a key intermediate for the diastereoselective preparation of a range of hydroxylated aminoazepanes was also demonstrated, including the synthesis of the *syn*-diastereomer of the balanol core. These studies have shown how the combination of an efficient multi-step tandem process followed by substrate directed reactions of the tetrahydroaminoazepine ring system can allow rapid access to highly functionalised azepane analogues. Work is currently underway to fully explore the asymmetric functionalisation of the chiral 2,3,6,7-tetrahydro-3-amidoazepines for the preparation of more complex compounds with potential biological application.

Experimental

Reactions were performed in flame-dried glassware under a positive atmosphere of argon. All reagents and starting materials were obtained from commercial sources and used as received. Dry solvents were purified using a PureSolv 500 MD solvent purification system or tetrahydrofuran and diethyl ether were distilled from sodium and benzophenone, whilst dichloromethane was distilled from calcium hydride. Flash column chromatography was carried out using Fisher matrix silica 60. Macherey–Nagel aluminium-backed plates pre-coated with silica gel 60 (UV_{254}) were used for thin layer chromatography and were visualised by staining with $KMnO_4$. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker DPX 400 spectrometer with chemical shift values in ppm relative to TMS (δ_H 0.00 and δ_C 0.0) or residual chloroform (δ_H 7.28 and δ_C 77.2) as standard. Assignment of ^{1}H and ^{13}C NMR signals are based on two-dimensional COSY and DEPT experiments, respectively. Mass spectra were obtained using a JEOL JMS-700 spectrometer. Infrared spectra were recorded using Golden Gate apparatus on a JASCO FTIR 410. Melting points were determined on a Reichert platform melting point apparatus. Optical rotations were determined as solutions irradiating with the sodium D line (λ = 589 nm) using an Auto pol V polarimeter. $[\alpha]_D$ values are given in units 10^{-1} deg cm^2 g^{-1}. The chiral HPLC methods were calibrated with their corresponding racemic mixtures. (*S*)-COP-Cl **22** refers to di-μ-chlorobis[η^5-(*S*)-($_{\rho}$*R*)-2-(2’-(4’-methylethyl)oxazolinyl)cyclopentadienyl, 1-*C*, 3’-*N*)(η^4-tetraphenylcyclobutadiene)cobalt]dipalladium and (*R*)-COP-Cl refers to di-μ-chlorobis[η^5-(*R*)-($_{\rho}$*R*)-2-(2’-(4’-methylethyl)oxazolinyl)cyclopentadienyl, 1-*C*, 3’-*N*)(η^4-tetraphenylcyclobutadiene)cobalt]dipalladium.

N-[2′-(*tert*-Butyldiphenylsilyloxy)ethyl]-1-aminobut-3-ene

Sodium iodide (0.55 g, 3.70 mmol) was added to a solution of 4-bromo-1-butene (5.00 g, 37.1 mmol) and 2-aminoethanol (**6**) (8.85 mL, 185.3 mmol) in methanol (80 mL). The reaction mixture was heated under reflux for 2 h, then cooled to room temperature and evaporated *in vacuo*. The residue was partitioned between saturated aqueous ammonium chloride solution (20 mL) and ethyl acetate (20 mL). The aqueous layer was made basic with 40% sodium hydroxide and extracted with ethyl acetate (3 × 15 mL). The combined organic layers were dried ($MgSO_4$) and concentrated to afford *N*-[2′-(hydroxy)ethyl]-1-aminobut-3-ene (**7**) (4.26 g, 100% yield) as a colourless oil. This oil was dissolved in tetrahydrofuran (200 mL) and *tert*-butyldiphenylsilyl chloride (14.44 mL, 55.6 mmol) and imidazole (5.04 g, 74.1 mmol) were added. The reaction mixture was stirred overnight at room temperature. A white precipitate was removed by filtration and washed with diethyl ether (70 mL). The combined filtrate was concentrated, dried ($MgSO_4$) and purified by flash column chromatography on silica gel (elution with dichloromethane/ethyl acetate, 1:5) to give *N*-[2′-(*tert*-butyldimethylsilyloxy)ethyl]-1-aminobut-3-ene (9.43 g, 86%) as a colourless oil. υ_{max}/cm^{-1} (neat) 3071 (NH), 2932 (CH), 1465, 1080, 910, 702; δ_H (400 MHz, $CDCl_3$) 1.08 (9H, s, $SiC(CH_3)_3$), 2.31 (2H, qt, *J* 6.8, 0.8 Hz, 2-H_2), 2.72 (2H, t, *J* 6.8 Hz, 1-H_2), 2.79 (2H, t, *J* 5.4 Hz, 1′-H_2), 3.81 (2H, t, *J* 5.4 Hz, 2′-H_2), 5.06–5.18 (2H, m, 4-H_2), 5.17 (1H, ddt, *J* 17.1, 10.2, 6.8 Hz, 3-H), 7.38–7.49 (6H, m, ArH), 7.68–7.72 (4H, m, ArH); δ_C (101 MHz, $CDCl_3$) 19.2 (C), 26.9 (3 × CH_3), 34.4 (CH_2), 48.6 (CH_2), 51.5 (CH_2), 63.1 (CH_2), 116.4 (CH_2), 127.7 (4 × CH), 129.7 (2 × CH), 133.7 (2 × C), 135.6 (4 × CH), 136.5 (CH); *m/z* (CI) 354.2254 (MH^+. $C_{22}H_{32}NOSi$ requires 354.2253), 312 (6%), 257 (8), 193 (5), 137 (7), 113 (28), 85 (89), 69 (100).

N-2′-(*tert*-Butyldiphenylsilyloxy)ethyl-*N*-(*tert*-butoxycarbonyl)-1-aminobut-3-ene (8)

To a solution of *N*-[2′-(*tert*-butyldimethylsilyloxy)ethyl]-1-aminobut-3-ene (4.00 g, 11.3 mmol) in dichloromethane (100 mL) at 0 °C was added triethylamine (3.31 mL, 23.7 mmol), 4-dimethylaminopyridine (0.14 g, 1.30 mmol) and di-*tert*-butyl dicarbonate (4.93 g, 22.6 mmol). The reaction mixture was warmed to room temperature and stirred overnight. The reaction mixture was washed with brine (2 × 30 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (elution with ethyl acetate/diethyl ether, 1:10) gave *N*-2′-(*tert*-butyldiphenylsilyloxy)ethyl-*N*-(*tert*-butoxycarbonyl)-1-aminobut-3-ene (**8**) (5.1 g, 100%) as a colourless oil. υ_{max}/cm^{-1} (neat) 2932 (CH), 1690 (CO), 1474, 1412, 1265, 1157, 1111, 825; NMR spectra showed a 1:1 mixture of rotomers, only signals for one rotomer is recorded: δ_H (400 MHz, $CDCl_3$) 1.05 (9H, s, $SiC(CH_3)_3$), 1.37 (9H, s, $OC(CH_3)_3$), 2.20–2.29 (2H, m, 2-H_2), 3.25–3.40 (4H, m, 1-H_2 and 1′-H_2), 3.25–3.39 (2H, m, 2′-H_2), 4.96–5.06 (2H, m, 4-H_2), 5.66–5.81 (1H, m, 3-H), 7.33–7.44 (6H, m, ArH), 7.63–7.67 (4H, m, ArH); δ_C (101 MHz, $CDCl_3$) 19.2 (C), 26.9 (3 × CH_3), 28.5 (3 × CH_3), 32.7 (CH_2), 45.6 (CH_2), 49.5 (CH_2), 62.5 (CH_2), 83.0 (C), 116.4 (CH_2), 127.7 (4 × CH), 129.7 (2 × CH), 133.6 (2 × C), 135.3 (4 × CH), 135.8 (CH), 155.4 (C); *m/z* (CI) 454.2772 (MH^+. $C_{27}H_{40}NO_3Si$ requires 454.2777), 398 (18%), 354 (28), 340 (12), 320 (8), 257 (8), 179 (5), 139 (6), 97 (28), 85 (87), 69 (100).

N-2′-(Hydroxy)ethyl-*N*-(*tert*-butoxycarbonyl)-1-aminobut-3-ene (9)

A solution of *n*-tetrabutylammonium fluoride (1.0 M in tetrahydrofuran) (13.6 mL, 13.6 mmol) was added to a solution of *N*-2′-(*tert*-butyldiphenylsilyloxy)ethyl-*N*-(*tert*-butoxycarbonyl)-1-aminobut-3-ene (**8**) (5.12 g, 11.3 mmol) in tetrahydrofuran (100 mL) at 0 °C. The reaction mixture was warmed to room temperature and stirred overnight. The reaction mixture was then concentrated and the resulting residue was re-suspended in diethyl ether (80 mL). The solution was washed with water (40 mL) and the aqueous layer was then extracted with diethyl ether (3 × 40 mL). The combined organic extracts were dried ($MgSO_4$), concentrated and then purified by flash column chromatography (petroleum ether/diethyl ether, 1:5) to give *N*-2′-(hydroxy)ethyl-*N*-(*tert*-butoxycarbonyl)-1-aminobut-3-ene (**9**) (2.42 g, 100%) as a colourless oil. υ_{max}/cm^{-1} (neat) 3742 (OH), 2978 (CH), 1690 (CO), 1474, 1412, 1250, 1157, 910, 733; δ_H (400 MHz, $CDCl_3$) 1.48 (9H, s, $OC(CH_3)_3$), 2.30 (2H, q, *J* 6.8 Hz, 2-H_2), 3.25–3.35 (2H, m, 1-H_2), 3.40 (2H, t, *J* 4.8 Hz, 1′-H_2), 3.80 (2H, t, *J* 4.8 Hz, 2′-H_2), 5.03–5.12 (2H, m, 4-H_2), 5.71–5.84 (1H, m, 3-H); δ_C (101 MHz, $CDCl_3$) 28.4 (3 × CH_3), 33.3 (CH_2), 48.5 (CH_2), 50.6 (CH_2), 62.8 (CH_2), 80.2 (C), 116.8 (CH_2), 135.3 (CH), 155.5 (C); *m/z* (CI) 216.1603 (MH^+. $C_{11}H_{22}NO_3$ requires 216.1600), 202 (5%), 174 (8), 160 (100), 116 (6), 85 (21), 69 (28).

Ethyl (2′*E*)-*N*-(butyl-3-en-1-yl)-*N*-(*tert*-butoxycarbonyl)-1′-aminobut-2′-enoate (11)

Dimethyl sulfoxide (2.36 mL, 33.2 mmol) was added to a stirred solution of oxalyl chloride (1.58 mL, 18.6 mmol) in dichloromethane (50 mL) at –78 °C. The reaction mixture was stirred for 0.3 h before *N*-2′-(hydroxy)ethyl-*N*-(*tert*-butoxycarbonyl)-1-aminobut-3-ene (**9**) (2.86 g, 13.3 mmol) in dichloromethane (50 mL) was slowly added. The mixture was stirred for a further 0.3 h before triethylamine (9.27 mL, 66.5 mmol) was added. This reaction mixture was stirred for 0.5 h at –78 °C and then allowed to warm to room temperature and stirred for a further 2 h. Meanwhile, a solution of lithium chloride (1.01 g, 23.9 mmol), triethyl phosphonoacetate (4.75 mL, 23.9 mmol) and 1,8-diazabicyclo[5,4,0]undec-7-ene (3.58 mL, 23.9 mmol) in acetonitrile (100 mL) was prepared and stirred for 1.0 h. The Swern solution was concentrated *in vacuo*, then the Horner-Wadsworth-Emmons solution was added and the reaction mixture was stirred at room temperature overnight. The reaction was quenched by the addition of a saturated solution of ammonium chloride (50 mL) and concentrated to give an orange residue, which was then extracted with diethyl ether (4 × 75 mL). The organic layers were combined, dried ($MgSO_4$) and concentrated to give an orange oil. Purification by flash column chromatography (diethyl ether/petroleum ether, 2:3) gave ethyl (2′*E*)-*N*-(butyl-3-en-1-yl)-*N*-(*tert*-butoxycarbonyl)-1′-aminobut-2′-enoate (**11**) (2.90 g, 94%) as colourless oil. υ_{max}/cm^{-1} (NaCl) 2978 (CH), 1690 (CO), 1466, 1412, 1366, 1273, 1165, 910, 725; NMR spectra showed a 1:1 mixture of rotomers, only signals for one rotomer is recorded: δ_H (400 MHz, $CDCl_3$) 1.32 (3H, t, *J* 7.3 Hz, OCH_2CH_3), 1.49 (9H, s, $OC(CH_3)_3$), 2.25–2.35 (2H, m, 2-H_2), 3.19–3.36 (2H, m, 1-H_2), 3.93–4.06 (2H, m, 1′-H_2), 4.23 (2H, q, *J* 7.3 Hz, OCH_2CH_3), 5.02–5.14 (2H, m, 4-H_2), 5.71–5.80 (1H, m, 3-H), 5.88 (1H, dt, *J* 15.6, 1.8 Hz, 3′-H), 6.89 (1H, dt, *J* 15.6, 4.7 Hz, 2′-H); δ_C (101 MHz, $CDCl_3$) 14.2 (CH_3), 28.4 (3 × CH_3), 33.1 (CH_2), 46.8 (CH_2), 47.8 (CH_2), 60.5 (CH_2), 80.0 (C), 116.9 (CH_2), 121.8 (CH), 135.2 (CH), 144.2 (CH), 155.3 (C), 166.1 (C); *m/z* (CI) 284.1862 (MH^+. $C_{15}H_{26}NO_4$ requires 284.1862), 228 (94%), 184 (62), 142 (10) 113 (32), 97 (35), 85 (82), 71 (100).

(2*E*)-*N*-(Butyl-3-en-1-yl)-*N*-(*tert*-butoxycarbonyl)-1′-aminobut-2′-en-4′-ol (5)

A stirred solution of (2′*E*)-*N*-(butyl-3-en-1-yl)-*N*-(*tert*-butoxycarbonyl)-1′-aminobut-2′-enoate (**11**) (0.25 g, 0.90 mmol) in dichloromethane (30 mL) was cooled to –78 °C before boron trifluoride diethyl etherate (0.15 mL, 1.17 mmol) was added dropwise. The mixture was stirred at –78 °C for 0.5 h before diisobutylaluminium hydride solution (1.0 M in hexanes, 2.7 mL, 2.7 mmol) was added dropwise. The reaction mixture was then stirred at –78 °C for 3 h before being quenched by the addition of 5.0 M acetic acid solution in dichloromethane (10 mL). The mixture was poured into 10% aqueous tartaric acid solution (10 mL), and the organic layers were extracted using dichloromethane (2 × 20 mL). The combined organic layers were washed with a saturated aqueous solution of sodium hydrogen carbonate (15 mL) before being dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude product was purified by flash column chromatography (petroleum ether/diethyl ether, 2:5) to give (2*E*)-*N*-(butyl-3-en-1-yl)-*N*-(*tert*-butoxycarbonyl)-1′-aminobut-2′-en-4′-ol (**5**) (0.09 g 41%) as a colourless oil. υ_{max}/cm^{-1} (neat) 3433 (OH), 2978 (CH), 1674 (CO), 1474, 1412, 1366, 1242, 1165, 918; δ_H (400 MHz, $CDCl_3$) 1.38 (9H, s, $OC(CH_3)_3$), 2.18 (2H, q, *J* 7.5 Hz, 2-H_2), 3.06–3.22 (2H, m, 1-H_2), 3.66–3.79 (2H, m, 1′-H_2), 4.13 (2H, d, *J* 4.1 Hz, 4′-H_2), 4.89–5.02 (2H, m, 4-H_2), 5.49–5.76 (3H, m, 3-H, 2′-H and 3′-H); δ_C (101 MHz, $CDCl_3$) 28.5 (3 × CH_3), 32.5 (CH_2), 46.3 (CH_2), 48.3 (CH_2), 63.1 (CH_2), 79.5 (C), 116.5 (CH_2), 127.9 (CH), 131.0 (CH), 135.5 (CH), 155.4 (C); *m/z* (CI) 242.1752 (MH^+. $C_{13}H_{24}NO_3$ requires 242.1756), 224 (8%), 200 (9), 186 (100), 168 (72), 160 (12), 113 (14), 85 (28), 73 (38).

***N*-(2′-Oxoethyl)-*N*-(*tert*-butoxycarbonyl)-1-aminobut-3-ene (10)**

Dimethyl sulfoxide (4.20 mL, 59.2 mmol) was added to a stirred solution of oxalyl chloride (3.10 mL, 35.5 mmol) in dichloromethane (50 mL) at –78 °C. The reaction mixture was stirred for 0.3 h before *N*-2′-(hydroxy)ethyl-*N*-(*tert*-butoxycarbonyl)-1-aminobut-3-ene (**9**) (5.10 g, 23.7 mmol) in dichloromethane (25 mL) was slowly added. The mixture was stirred for a further 0.3 h before triethylamine (16.5 mL, 118.4 mmol) was added. This reaction mixture was stirred for 0.5 h at –78 °C and then allowed to warm to room temperature and stirred for a further 2 h. The reaction mixture was concentrated *in vacuo*, and purified by flash column chromatography (petroleum ether/diethyl ether, 2:5) to give *N*-(2′-oxoethyl)-*N*-(*tert*-butoxycarbonyl)-1-aminobut-3-ene (**10**) (4.74 g, 94%) as a colourless oil. υ_{max}/cm^{-1} (neat) 2982 (CH), 1736 (CO), 1686 (CO), 1424, 1370, 1216, 1153, 907, 729; NMR spectra showed a 1:1 mixture of rotomers, only signals for one rotomer is recorded: δ_H (400 MHz, $CDCl_3$) 1.45 (9H, s, $OC(CH_3)_3$), 2.23–2.33 (2H, m, 2-H_2), 3.30 (2H, t, *J* 7.1 Hz, 1-H_2), 3.80 (2H, br s, 1′-H_2), 5.02–5.11 (2H, m, 4-H_2), 5.68–5.83 (1H, m, 3-H), 9.56 (1H, br s, 2’-H); δ_C (101 MHz, $CDCl_3$) 28.2 (3 × CH_3), 33.0 (CH_2), 48.5 (CH_2), 57.7 (CH_2), 80.8 (C), 117.2 (CH_2), 135.1 (CH), 155.0 (C), 199.4 (C); *m/z* (CI) 214.1440 (MH^+. $C_{11}H_{20}NO_3$ requires 214.1443), 200 (10%), 196 (8), 158 (100), 114 (9), 85 (7), 69 (12).

(2′*E*)-*N*-(Butyl-3-en-1-yl)-*N*-(*tert*-butoxycarbonyl)-1′-aminobut-2′-en-4′-al (12).

To a solution of *N*-(2′-oxoethyl)-*N*-(*tert*-butoxycarbonyl)-1-aminobut-3-ene (**10**) (1.60 g, 7.51 mmol) in toluene (80 mL) was added (triphenylphosphoranylidene)acetaldehyde (3.42 g, 11.3 mmol) and the reaction mixture was heated at 80 °C and stirred for 24 h. The solution was allowed to cool to room temperature and concentrated *in vacuo*. The resulting residue was purified with flash column chromatography (petroleum ether/diethyl ether, 2:5) to give (2′*E*)-*N*-(butyl-3-en-1-yl)-*N*-(*tert*-butoxycarbonyl)-1′-aminobut-2′-en-4′-al (**12**) (1.35 g, 75%) as colourless oil. υ_{max}/cm^{-1} (neat) 2982 (CH), 2361, 1678 (CO), 1416, 1215, 1169, 918, 745; NMR spectra showed a 1:1 mixture of rotomers, only signals for one rotomer is recorded: δ_H (400 MHz, $CDCl_3$) 1.51 (9H, s, $OC(CH_3)_3$), 2.26–2.36 (2H, m, 2-H_2), 3.22–3.38 (2H, m, 1-H_2), 4.05–4.19 (2H, m, 1′-H_2), 5.05–5.15 (2H, m, 4-H_2), 5.71–5.85 (1H, m, 3-H), 6.17 (1H, ddt, *J* 15.8, 7.9, 1.6 Hz, 3′-H), 6.72–6.86 (1H, m, 2′-H), 9.62 (1H, d, *J* 7.9 Hz, 4’-H); δ_C (101 MHz, $CDCl_3$) 28.4 (3 × CH_3), 33.2 (CH_2), 47.2 (CH_2), 48.3 (CH_2), 80.3 (C), 117.0 (CH_2), 125.3 (CH), 129.1 (CH), 132.3 (CH), 153.4 (C), 193.2 (C); *m/z* (CI) 240.1595 (MH^+. $C_{13}H_{22}NO_3$ requires 240.1600), 236 (19%), 210 (96), 184 (100), 158 (40), 116 (58), 69 (12).

(2*E*)-*N*-(Butyl-3-en-1-yl)-*N*-(*tert*-butoxycarbonyl)-1′-aminobut-2′-en-4′-ol (5)

To a solution of (2′*E*)-*N*-(butyl-3-en-1-yl)-*N*-(*tert*-butoxycarbonyl)-1′-aminobut-2′-en-4′-al (**12**) (0.30 g, 1.28 mmol) in methanol (35 mL) at 0 °C was added sodium borohydride (0.09 g, 2.56 mmol). After 1 h, the reaction mixture was quenched with 1.0 M hydrochloric acid (5 mL) and then concentrated *in vacuo.* The residue was dissolved in dichloromethane (20 mL), washed with saturated sodium hydrogencarbonate solution (10 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The crude product was purified by flash column chromatography (petroleum ether/diethyl ether, 2:5) to give (2*E*)-*N*-(butyl-3-en-1-yl)-*N*-(*tert*-butoxycarbonyl)-1′-aminobut-2′-en-4′-ol (**5**) (0.26 g 88%) as a colourless oil. Spectroscopic data as reported above.

1-(*tert*-Butoxycarbonyl)-2,3,6,7-tetrahydro-3-(2′,2′,2′-trichloromethylcarbonylamino)azepine (4)

(2*E*)-*N*-(Butyl-3-en-1-yl)-*N*-(*tert*-butoxycarbonyl)-1′-aminobut-2′-en-4′-ol (**5**) (0.13 g, 0.54 mmol) was dissolved in dichloromethane (20 mL) and cooled to 0 °C. 1,8-Diazabicyclo[5.4.0]undec-7-ene (0.02 mL, 0.14 mmol) was added to the solution followed by trichloroacetonitrile (0.08 mL, 0.81 mmol). The reaction mixture was then warmed to room temperature and stirred for 2 h. The reaction mixture was filtered through a short pad of silica gel and washed with diethyl ether (100 mL). The resulting filtrate was then concentrated to give allylic trichloroacetimidate **13**, which was used without further purification. Allylic trichloroacetimidate **13** was then dissolved in dichloromethane (10 mL). Bis(acetonitrile)palladium(II) chloride (0.014 g, 0.05 mmol) was added to the solution and the reaction mixture was stirred at room temperature for 3 h. Grubbs first generation catalyst (0.044 g, 0.05 mmol) was then added and the reaction mixture was heated under reflux for 96 h. The reaction mixture was cooled to room temperature and then filtered through a short pad of Celite® and washed with diethyl ether (100 mL). Concentration of the filtrate, followed by flash column chromatography (petroleum ether/diethylether, 2:1) gave 1-(*tert*-butoxycarbonyl)-2,3,6,7-tetrahydro-3-(2′,2′,2′-trichloromethylcarbonylamino)azepine (**4**) (0.09 g, 49% over three steps) as a white solid. Mp 103–105 °C; υ_{max}/cm^{-1} (NaCl) 3330 (NH), 2978 (CH), 1690 (CO), 1419, 1366, 1165, 756; NMR spectra showed a 1:1 mixture of rotomers, only signals for one rotomer is recorded: δ_H (400 MHz, $CDCl_3$) 1.47 (9H, s, $OC(CH_3)_3$), 2.17–2.42 (2H, m, 6-H_2), 3.03–3.16 (1H, m, 7-*H*H), 3.32 (1H, dd, *J* 14.9, 2.6 Hz, 2-*H*H), 3.72–3.81 (1H, m, 7-H*H*), 4.05 (1H, br d, *J* 14.9 Hz, 2-H*H*), 4.43–4.59 (1H, m, 3-H), 5.53–5.93 (2H, m, 4-H and 5-H), 8.30 (1H, br s, NH); δ_C (101 MHz, $CDCl_3$) 27.9 (CH_2), 28.4 (3 × CH_3), 47.7 (CH_2), 48.7 (CH_2), 54.2 (CH), 80.7 (C), 92.1 (C), 128.6 (CH), 129.5 (CH), 157.2 (C), 163.7 (C); *m/z* (CI) 359.0511 (MH^+. $C_{13}H_{20}{}^{35}Cl_2{}^{37}ClN_2O_3$ requires 359.0512), 301 (100%), 267 (34), 257 (18), 223 (7), 163 (8), 85 (13), 69 (19).

1-(*tert*-Butoxycarbonyl)-2,3,6,7-tetrahydro-3-(2′,2′,2′-trichloromethylcarbonylamino)azepine (4)

The reaction was carried out as described above except using (2*E*)-*N*-(butyl-3-en-1-yl)-*N*-(*tert*-butoxycarbonyl)-1′-aminobut-2′-en-4′-ol (**5**) (0.13 g, 0.54 mmol) and Grubbs second generation catalyst (0.044 g, 0.05 mmol) for the RCM step which was complete in 12 h. Purification by flash column chromatography (petroleum ether/diethylether, 2:1) gave 1-(*tert*-butoxycarbonyl)-2,3,6,7-tetrahydro-3-(2′,2′,2′-trichloromethylcarbonylamino)azepine (**4**) (0.15 g, 79% over three steps) as a white solid. Spectroscopic data as reported above.

2′,2′,2′-Trichloro-*N*-[(3*S,3a*S**,4a*R**)-1-*tert*-butoxycarbonylamino-4-oxobicyclo[5.1.0]octa-3a-yl]acetamide (15)**

1-(*tert*-Butoxycarbonyl)-2,3,6,7-tetrahydro-3-(2′,2′,2′-trichloromethylcarbonylamino)azepine (**4**) (0.19 g, 0.53 mmol) was dissolved in dichloromethane (15 mL) and to the stirred suspension was added *meta*-chloroperoxybenzoic acid (0.18 g 1.05 mmol) at room temperature. The resulting suspension was stirred vigorously for 19 h. A 20% aqueous solution of sodium sulfite (10 mL) was added and the resulting two-phase mixture was stirred vigorously for 0.25 h. The two layers were separated and the aqueous layer was extracted with dichloromethane (2 × 20 mL). The combined organic layers were washed with a 20% aqueous solution of sodium sulfite (10 mL) and a 5% aqueous solution of sodium hydrogencarbonate (2 × 20 mL), dried ($MgSO_4$) and evaporated under reduced pressure. Purification by flash column chromatography (elution with petroleum ether/diethyl ether, 2:5) gave 2′,2′,2′-trichloro-*N*-[(3*S**,3a*S**,4a*R**)-1-*tert*-butoxycarbonylamino-4-oxobicyclo[5.1.0]octa-3a-yl]acetamide (**15**) (0.11 g, 58%) as white solid. Mp 160–162 °C; υ_{max}/cm^{-1} (NaCl) 3293 (NH), 2974 (CH), 1697 (CO), 1518, 1414, 1368, 1165, 943, 821; NMR spectra showed a 2:1 mixture of rotomers, only signals for major rotomer is recorded: δ_H (400 MHz, $CDCl_3$) 1.50 (9H, s, $OC(CH_3)_3$), 2.21–2.37 (2H, m, 5-H_2), 2.78–2.93 (1H, m, 2-H_2), 3.26–3.33 (2H, m, 6-H_2), 3.83 (1H, dd, *J* 13.6, 4.4 Hz, 3a-H), 3.86–3.93 (1H, m, 4a-H), 4.59 (1H, td, *J* 9.2, 4.4 Hz, 3-H), 6.90 (1H, br d, *J* 9.2 Hz, NH); δ_C (101 MHz, $CDCl_3$) 27.6 (CH_2), 28.4 (3 × CH_3), 43.2 (CH_2), 46.5 (CH_2), 50.7 (CH), 55.4 (CH), 58.7 (CH), 80.7 (C), 92.3 (C), 154.3 (C), 161.4 (C); *m/z* (CI) 375.0453 (MH^+. $C_{13}H_{20}{}^{35}Cl_2{}^{37}ClN_2O_4$ requires 375.0461), 319 (100%), 283 (76), 273 (10), 239 (8), 211 (8), 155 (10), 81 (6), 69 (11).

(3*S,4*R**)-3-Aminoazepin-4-ol (17)[8h]**

2′,2′,2′-Trichloro-*N*-[(3*S**,3a*S**,4a*R**)-1-*tert*-butoxycarbonylamino-4-oxobicyclo[5.1.0]octa-3a-yl]acetamide (**15**) (0.05 g, 0.14 mmol) was dissolved in tetrahydrofuran (10 mL) and cooled to 0 °C. Lithium aluminium hydride (0.03 g, 0.71 mmol) was then added and the slurry was heated under reflux for 12 h. The solution was cooled to room temperature and concentrated *in vacuo*. The crude material was dissolved in methanol (2 mL) and 6.0 N hydrochloric acid (2 mL) was added. The reaction mixture was stirred at room temperature for 12 h and then concentrated *in vacuo*. Purification by ion exchange column chromatography (Dowex® 50WX8-100), eluting with 0.5 M ammonia solution gave (3*S**,4*R**)-3-aminoazepin-4-ol (**17**) (0.01 g 61% over two steps) as a viscous oil. Spectroscopic data as previously reported.[8h] υ_{max}/cm^{-1} (neat) 3369 (NH/OH), 2922 (CH), 1637, 1544, 1463, 1016; δ_H (500 MHz, $CDCl_3$) 1.86–1.96 (2H, m, 6-H_2), 2.17–2.25 (1H, m, 5-*H*H), 2.42–2.48 (1H, m, 2-*H*H), 2.57 (1H, td, *J* 10.0, 1.8 Hz, 7-*H*H), 2.76–2.86 (2H, m, 2-H*H* and 5-H*H*), 3.09–3.14 (2H, m, 4-H and 7-H*H*), 3.17–3.21 (1H, m, 3-H); δ_C (126 MHz, $CDCl_3$) 29.7 (CH_2), 31.7 (CH_2), 45.3 (CH_2), 54.3 (CH), 54.5 (CH_2), 62.3 (CH); *m/z* (CI) 131 (MH^+, 4%), 121 (100), 117 (70), 113 (15), 85 (18), 61 (19).

(3*S,4*S**,5*R**)-1-(*tert*-Butoxycarbonyl)-3-(2′,2′,2′-trichloromethylcarbonylamino)-4,5-dihydroxyazepane (18)**

1-(*tert*-Butoxycarbonyl)-2,3,6,7-tetrahydro-3-(2′,2′,2′-trichloromethylcarbonylamino)azepine (**4**) (0.048 g, 0.134 mmol) was dissolved in dichloromethane (8 mL) at –78 °C. Tetramethylethylenediamine (0.024 mL, 0.147 mmol) was added and the reaction mixture stirred for 0.1 h before the addition of osmium tetroxide (0.04 g, 0.157 mmol). The dark coloured solution was stirred for 1 h at –78 °C before warming to room temperature. The reaction mixture was stirred for a further 1 h. The solvent was removed *in vacuo* and the dark coloured solid was dissolved in 1:1 mixture of tetrahydrofuran and a saturated solution of aqueous sodium sulfite (10 mL). The reaction mixture was stirred and heated under reflux for 12 h. The solvent was removed *in vacuo* to afford a dark solid. Flash column chromatography (elution with ethyl acetate) afforded (3*S**,4*S**,5*R**)-1-(*tert*-butoxycarbonyl)-3-(2′,2′,2′-trichloromethyl carbonylamino)-4,5-dihydroxyazepane (**18**) (0.042 g, 81%) as a white solid. Mp 153–155 °C; υ_{max}/cm^{-1} (NaCl) 3390 (NH/OH), 2967 (CH), 1672 (CO), 1471, 1249, 956; NMR spectra showed a 1:1 mixture of rotomers, only signals for one rotomer is recorded: δ_H (400 MHz, $CDCl_3$) 1.45 (9H, s, $OC(CH_3)_3$), 1.64–1.75 (1H, m, 6-*H*H), 2.06–2.17 (1H, m, 6-H*H*), 2.77 (1H, br s, OH), 3.25–3.92 (4H, m, 4-H, 5-H and 7-H_2), 4.11–4.31 (2H, m, 2-H_2), 4.67–4.79 (1H, m, 3-H), 5.37 (1H, br s, NH); δ_C (126 MHz, $CDCl_3$) 28.4 (3 × CH_3), 29.7 (CH_2), 31.6 (CH_2), 47.6 (CH_2), 53.1 (CH), 70.1 (CH), 77.3 (CH), 80.6 (C), 92.3 (C), 155.4 (C), 158.4 (C); *m/z* (EI) 390.0523 (M^+. $C_{13}H_{21}{}^{35}Cl_3N_2O_5$ requires 390.0516), 354 (11%), 339 (20), 283 (8), 216 (28), 191 (100), 172 (9), 111 (18), 83 (35), 57 (98).

(3*S,4*S**,5*R**)-3-Aminoazepane-4,5-diol (19)**

To a solution of (3*S**,4*S**,5*R**)-1-(*tert*-butoxycarbonyl)-3-(2′,2′,2′-trichloromethylcarbonylamino)-4,5-dihydroxyazepane (**18**) (0.023 g, 0.051 mmol) in methanol (5 mL) was added 2.0 M sodium hydroxide (3 mL) and the reaction mixture was stirred at 40 °C for 12 h. 2.0 M Hydrochloric acid (10 mL) was added and the reaction was stirred for 1 h. The reaction mixture was concentrated *in vacuo*. The resulting residue was dissolved in chloroform (20 mL) and washed with water (10 mL). The organic layer was dried ($MgSO_4$) and concentrated under vacuum to give (3*S**,4*S**,5*R**)-3-aminoazepane-4,5-diol (**19**) as a white solid (0.07 g, 78%). Mp 172–174 °C (decomposition); υ_{max}/cm^{-1} (NaCl) 3379 (NH/OH), 2931 (CH), 1649, 1448, 1211, 970; δ_H (500 MHz, D_2O) 2.33–2.41 (1H, m, 6-*H*H), 2.49–2.61 (1H, m, 6-H*H*), 3.51–3.60 (1H, m, 7-*H*H), 3.80–3.88 (2H, m, 2-*H*H and 7-H*H*), 3.96–4.04 (1H, m, 3-H), 4.29–4.40 (2H, m, 2-H*H* and 5-H), 4.59–4.65 (1H, m, 4-H); δ_C (126 MHz, CD_3OD) 28.4 (CH_2), 43.4 (CH_2), 43.6 (CH_2), 50.0 (CH), 72.0 (CH), 73.0 (CH); *m/z* (CI) 147.1140 (MH^+. $C_6H_{15}N_2O_2$ requires 147.1133), 127 (100), 113 (4), 101 (12), 81 (8), 69 (11).

(3a*S,8*S**,8a*S**)-1-Oxo-2-trichloromethyl-3,5-diaza-5-(*tert*-butoxycarbonyl)-8-iodo-1,3a,4,5,6,7,8,8a-octahydroazulene (20)**

To a solution of 1-(*tert*-butoxycarbonyl)-3-(2′,2′,2′-trichloromethylamino)azapin-4-ene (**4**) (0.05 g, 0.139 mmol) in chloroform (8 mL), *N*-iodosuccinimide (0.05 g, 0.230 mmol) was added and the mixture stirred for 18 h. The solvent was then removed *in vacuo*. The resulting residue was dissolved in ethyl acetate (20 mL) and the organic layer washed with water (4 × 30 mL). The organic layer was then dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by flash column chromatography (elution with petroleum ether/diethyl ether, 5:1) gave (3a*S**,8*S**,8a*S**)-1-oxo-2-trichloromethyl-3,5-diaza-5-(*tert*-butoxycarbonyl)-8-iodo-1,3a,4,5,6,7,8,8a-octahydroazulene (**20**) (0.052 g, 78%) as a white solid. Mp 130–133 °C; υ_{max}/cm^{-1} (NaCl) 2933 (CH), 1684 (CO), 1417, 1243, 1164, 754; δ_H (500 MHz, $CDCl_3$) 1.47 (9H, s, $OC(CH_3)_3$), 1.98–2.15 (1H, m, 7-*H*H), 2.25–2.39 (1H, m, 7-H*H*), 3.31–4.03 (4H, m, 6-H_2 and 4-H_2), 4.51–4.62 (1H, m, 8-H), 4.63–4.75 (1H, m, 3a-H), 5.26 (1H, t, *J* 8.2 Hz, 8a-H); δ_C (126 MHz, $CDCl_3$) 26.3 (CH_2), 28.4 (3 × CH_3), 29.9 (CH_2), 36.2 (CH), 48.1 (CH_2), 68.9 (CH), 80.6 (CH), 86.2 (C), 89.6 (C), 154.7 (C), 161.0 (C); *m/z* (CI) 482.9496 (MH^+. $C_{13}H_{19}{}^{35}Cl_3IN_2O_3$ requires 482.9506), 427 (38%), 393 (8), 301 (6), 199 (4), 164 (13), 100 (100).

(3*S,4*S**,5*S**)-3-Amino-5-iodoazepane-4-ol (21)**

To a solution of (3a*S**,8*S**,8a*S**)-1-oxo-2-trichloromethyl-3,5-diaza-5-(*tert*-butoxycarbonyl)-8-iodo-1,3a,4,5,6,7,8,8a-octahydroazulene (**20**) (0.047 g, 0.097 mmol) in methanol (5 mL) was added 0.5 M hydrochloric acid (5 mL) and the reaction mixture was stirred at room temperature for 0.5 h. The reaction mixture was then diluted with a saturated solution of sodium hydrogencarbonate (10 mL) and extracted with ethyl acetate (3 ×

20 mL). The organic layers were combined, dried ($MgSO_4$) and concentrated *in vacuo* to give (3*S**,4*S**,5*S**)-3-amino-5-iodoazepane-4-ol (**21**) (0.03 g, 77%) as a white solid. Mp 154–155 °C; υ_{max}/cm^{-1} (NaCl) 3450 (OH), 3337 (NH), 2957 (CH), 1665, 1463, 1272, 741; δ_H (500 MHz, CD_3OD) 2.21–2.29 (1H, m, 6-*H*H), 2.55–2.62 (1H, m, 6-H*H*), 3.36 (1H, dd, *J* 13.5, 3.2 Hz, 2-*H*H), 3.41–3.49 (2H, m, 7-H_2), 3.72 (1H, dd *J* 13.5, 10.0 Hz, 2-H*H*), 4.24 (1H, dt, *J* 10.0, 3.2 Hz, 3-H), 4.42–4.45 (1H, m, 4-H), 4.61 (1H, dt, *J* 6.1, 3.5 Hz, 5-H); δ_C (126 MHz, CD_3OD) 29.2 (CH_2), 30.7 (CH), 41.5 (CH_2), 45.9 (CH_2), 49.8 (CH), 74.8 (CH); *m/z* (CI) 257.0158 (MH^+. $C_6H_{14}IN_2O$ requires 257.0151), 217 (20), 173 (12), 146 (8), 113 (8), 73 (22).

(3*R*)-1-(*tert*-Butoxycarbonyl)-2,3,6,7-tetrahydro-3-(2′,2′,2′-trichloromethylcarbonylamino)azepine

(2*E*)-*N*-(Butyl-3-en-1-yl)-*N*-(*tert*-butoxycarbonyl)-1′-aminobut-2′-en-4′-ol (**5**) (0.07 g, 0.31 mmol) was dissolved in dichloromethane (15 mL) and cooled to 0 °C. 1,8-Diazabicyclo[5.4.0]undec-7-ene (0.06 mL, 0.47 mmol) was added to the solution followed by trichloroacetonitrile (0.05 mL, 0.47 mmol). The reaction mixture was then warmed to room temperature and stirred for 2 h. The reaction mixture was filtered through a short pad of silica gel and washed with diethyl ether (100 mL). The resulting filtrate was then concentrated to give allylic trichloroacetimidate **13**, which was used without further purification. Allylic trichloroacetimidate **13** was then dissolved in dichloromethane (10 mL). (*S*)-COP-Cl **22** (0.023 g, 0.016 mmol) was added to the solution and the reaction mixture was stirred at room temperature for 72 h. Grubbs second generation catalyst (0.03 g, 0.03 mmol) was then added and the reaction mixture was heated under reflux for 24 h. The reaction mixture was cooled to room temperature and then filtered through a short pad of Celite® and washed with diethyl ether (100 mL). Concentration of the filtrate, followed by flash column chromatography (petroleum ether/diethylether, 2:1) gave (3*R*)-1-(*tert*-butoxycarbonyl)-2,3,6,7-tetrahydro-3-(2′,2′,2′-trichloromethylcarbonylamino)azepine (0.10 g, 92% over three steps) as a white solid. Chiral HPLC (Chiralcel IB column) analysis using 5% isopropanol in hexane as the elution solvent indicated 92% ee. $[\alpha]_D^{26}$ –120.8 (*c* 1.0, $CHCl_3$). All other spectroscopic data as previously reported above for 1-(*tert*-butoxycarbonyl)-2,3,6,7-tetrahydro-3-(2′,2′,2′-trichloromethylcarbonylamino)azepine (**4**).

(3*S*)-1-(*tert*-Butoxycarbonyl)-2,3,6,7-tetrahydro-3-(2′,2′,2′-trichloromethylcarbonylamino)azepine

The reaction was performed as described above, except using (2*E*)-*N*-(butyl-3-en-1-yl)-*N*-(*tert*-butoxycarbonyl)-1′-aminobut-2′-en-4′-ol (**5**) (0.06 g, 0.26 mmol) and (*R*)-COP-Cl (0.019 g, 0.013 mmol). Purification by flash column chromatography (petroleum ether/diethylether, 2:1) gave (3*S*)-1-(*tert*-butoxycarbonyl)-2,3,6,7-tetrahydro-3-(2′,2′,2′-trichloromethylcarbonylamino)azepine (0.08 g, 84% over three steps) as a white solid. Chiral HPLC (Chiralcel IB column) analysis using 5% isopropanol in hexane as the elution solvent indicated 92% ee. $[\alpha]_D^{24}$ +140.7 (*c* 0.7, $CHCl_3$). All other spectroscopic data as previously reported above for 1-(*tert*-butoxycarbonyl)-2,3,6,7-tetrahydro-3-(2′,2′,2′-trichloromethylcarbonylamino)azepine (**4**).

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Notes and references

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† Electronic Supplementary Information (ESI) available: NOE data for compounds **15**, **18** and **20** and, [1]H and [13]C NMR spectra for all new compounds. See DOI: 10.1039/b000000x/

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