ARTICLE

OBC
www.rsc.org/obc

Chirality transfer in the aza-[2,3]-Wittig sigmatropic rearrangement†

James C. Anderson,*[a] J. Gair Ford[b] and Matthew Whiting[a]

[a] *School of Chemistry, University of Nottingham, Nottingham, UK NG7 2RD. E-mail: j.anderson@nottingham.ac.uk; Fax: +44(0)115 9513564; Tel: +44(0)115 9514194*

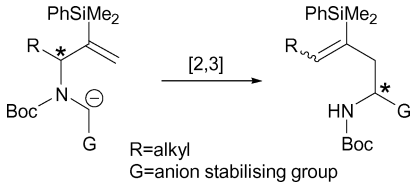
[b] *AstraZeneca Process R & D, Charter Way Silk Road Business Park, Macclesfield, Cheshire, UK SK10 2NA. E-mail: Gair.Ford@astrazeneca.com; Tel: +44(0)1625 513375*

Received 29th July 2005, Accepted 22nd August 2005
First published as an Advance Article on the web 12th September 2005

The aza-[2,3]-Wittig sigmatropic rearrangements of substrates derived from enantiomerically pure alanine, valine and serine with phenyl and ester anion stabilising groups were investigated for their efficiency in chirality transfer. It was found that a methyl substituent at the stereogenic centre of the rearrangement precursors was inadequate to control the alkene stereoselectivity and enantioselectivity of the rearrangement. Ester stabilised anions of valine and serine derivatives were the most successful with up to 66% yield, 14 : 1 alkene (*E*)-stereoselection and 88% chirality transfer. A limitation to the steric bulk of the stereogenic centre was noted in that the substituent has to be bulky enough to dictate alkene stereoselection, but not too large to compromise the directing effect of the activating phenyldimethyl silyl substituent on the anion stabilising group. Experimental evidence suggested a possible complimentary coordinating effect of an *O*–MOM serine substituent, which may assist alkene stereoselectivity and enantioselectivity.

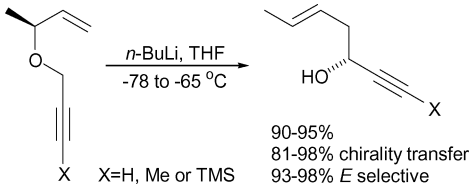
Introduction

We have detailed racemic studies into the aza-[2,3]-Wittig sigmatropic rearrangement which have shown it to be a useful method for the synthesis of certain unnatural amino acids[1] and that these can be used as building blocks in target synthesis.[2] More recently we have summarised some of our attempted strategies towards preparing enantiomerically pure aza-[2,3]-rearrangement products and detailed the use of (−)-8 phenylmenthol as a chiral auxiliary.[3] An (−)-8-phenylmenthol ester of a glycine derived migrating group controlled the absolute stereochemistry of aza-[2,3]-Wittig sigmatropic rearrangements with diastereoselectivities of ~3 : 1 with respect to the auxiliary and *ca.* 50% isolated yields of enantiomerically pure products. This chiral auxiliary approach was only moderately successful and we have been investigating alternative strategies to control stereoselectivity. This paper describes in detail our attempts to use internal chirality transfer to control the absolute stereochemistry of the aza-[2,3]-Wittig sigmatropic rearrangement (eqn. (1)).



(1)

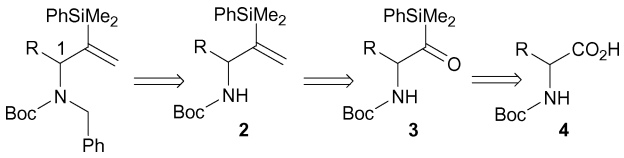
For the related oxy-[2,3]-Wittig rearrangement there are three main ways by which absolute stereochemistry has been controlled; asymmetric induction from a chiral auxiliary,[4] enantioselective rearrangements[5] and internal chirality transfer.[6,7] The closest examples to the strategy described in this current paper were in work carried out on 1,4 chirality transfer (eqn. (2)), where they observed 81–98% chirality transfer with 93–98% *E* selectivity, dependent upon the choice of anion stabilising group.[8] As far as we are aware there have been no studies investigating internal chirality transfer in the aza-[2,3]-Wittig sigmatropic rearrangement.



(2)

Results and discussion

Our preliminary study investigated the rearrangement of aza-[2,3]-Wittig precursors **1**. These precursors allowed us to investigate the steric properties of the substituent at the chiral C1 centre by comparing a methyl substituent with an isopropyl substituent. A terminal alkene was chosen so as to eliminate analysis of vicinal diastereoselectivity in the product and because differentiation between potentially competing [1,2] and the desired [2,3] rearrangement would be monitored by the C1 substituent. The phenyl group was chosen as the anion stabilising group as this was the most robust group available. Retrosynthesis of **1** led to vinyl silane **2** which could be derived by methylenation of acyl silane **3**, itself derived from *N*-Boc protected amino acid **4** (Scheme 1).



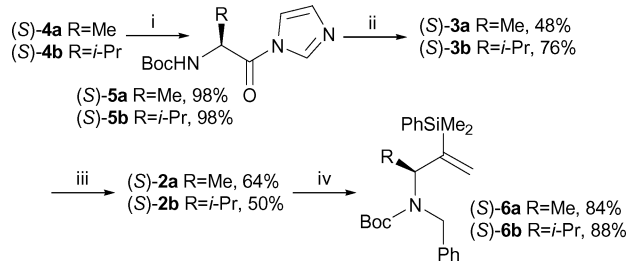
Scheme 1 Retrosynthesis.

The synthesis of acyl silanes has received considerable attention[9] and it has been shown that these can be prepared from *N*-Pht and *N*-Ts α-amino acid chlorides on treatment with a silylcuprate reagent without loss of enantiomeric purity.[10] However under the same reaction conditions, *N*-Boc protected amino acid chlorides have been shown to form the corresponding oxazoline through spontaneous intramolecular cyclisation.[11] This has been avoided in the synthesis of *N*-Boc-phenylalanine and *N*-Boc-isoleucine based acyl silanes by activation of the amino acids as their acyl imidazoles followed by reaction with $(Me_2PhSi)_2CuCNLi_2$.[12] To adopt this approach we treated *N*-Boc alanine and *N*-Boc valine

† This paper is dedicated to my friend and mentor Professor Steven V. Ley on the occasion of his 60th birthday.

DOI:10.1039/b510756c

with CDI (carbonyldiimidazole) to give the corresponding acylimidazoles (*S*)-**5a,b** (Scheme 2). The crude products were then treated with $(Me_2PhSi)_2CuCNLi_2$[13] to give the acyl silanes (*S*)-**3a,b** in 48% and 76% yields respectively. In the case of the lower yielding and sterically less demanding substrate (**5a**) a number of byproducts were observed which, although they could never be fully separated from themselves, appeared by characteristic peaks in their ^{1}H NMR spectra to be products of di-addition of the silyl nucleophile. Although the olefination of acyl silanes has been investigated using Wittig[14,15] and Peterson olefination[16] methods, α-branching, enolisation and competing Brook rearrangement severely reduced yields. We could find no precedent for the olefination of an acyl silane containing an enantiomerically pure α-chiral centre. We decided to use the non-basic Tebbe reagent[17] which had been shown to be suitable for the olefination of numerous carboxylic acid derivatives, including those containing readily enolisable α-protons.[18] Careful optimisation of the reaction conditions led to the use of 1.5 equiv. of Tebbe reagent in THF at −40 °C for 1–1.5 h only. This led to reproducible yields of vinyl silanes (*S*)-**2a,b** in reproducible isolated yields of 64% and 50% respectively in addition to recovered starting materials. The lower yield of the valine derived compound we attribute to increased steric bulk at the α-position hindering attack of the bulky titanium reagent. Prolonged reaction temperatures led to degradation of material probably caused by the highly Lewis acidic Me_2AlCl liberated during the Tebbe olefination. The use of the much milder Petasis reagent,[19] which has been used for the olefination of an acyl silane,[20] unfortunately gave complete degradation of material. Benzylation of the amines (*S*)-**2a,b** required the use of KH to effect efficient deprotonation which then gave (*S*)-**6a,b** in 84% and 88% yield respectively. The synthetic sequence (Scheme 2) was then repeated on the enantiomeric amino acid series and chiral HPLC analysis confirmed that no racemisation had occurred in the synthesis.[21]



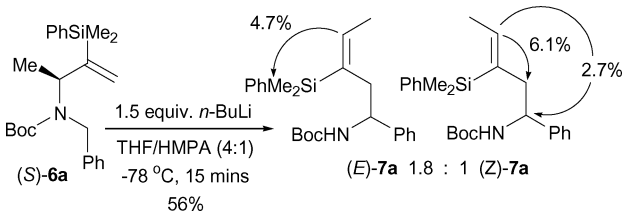
Scheme 2 *Reagents and conditions*: i, CDI, THF, 0 °C; ii, $(Me_2PhSi)_2CuCNLi_2$, THF, −78 °C; iii, $Cp_2Ti(CH_2)ClAlMe_2$, THF, −40 °C; iv, KH, THF, rt, 30 mins, then BnBr, TBAI, rt, 16 h.

Aza-[2,3]-Wittig sigmatropic rearrangement of the alanine derived precursor (*S*)-**6a** was achieved by using 1.5 equiv. *n*-BuLi in THF–HMPA (4 : 1) at −78 °C with quenching of the reaction after disappearance of starting material (TLC, 15 mins), with MeOH. This gave the rearranged product **7a** as a 1.8 : 1 mixture of inseparable *E* : *Z* diastereoisomers in 56% isolated yield (eqn. (3)). Lower quantities of *n*-BuLi gave incomplete conversion and higher reaction temperatures (−20 and 0 °C) gave rearrangement in less than 5 mins, but with a 1 : 1 mixture of alkene diastereoisomers. The *E* and *Z* alkenes were distinguished by selected one dimensional NOE experiments. Irradiation of the vinylic proton of (*E*)-**7a** (δ 6.07, 1H, q, $J = 6.5$ Hz) gave a 4.7% enhancement of the $SiMe_2$ signals (δ 0.35 and 0.37, 2 × 3H, s), whereas irradiation of the vinylic proton of (*Z*)-**7a** (δ 6.20, q, $J = 6.8$ Hz) gave a 6.1% enhancement of one of the CH_2 protons (δ 2.18–2.23, 1H, m) and a 2.7% enhancement of the benzylic CH (δ 4.52–4.75, 2H, m, N*H* + PhC*H*). At this preliminary stage we decided there was little to be gained from looking into the enantioselectivity of this reaction (eqn. (3)) as the alkene stereoselection was so poor. Instead we investigated the rearrangement of the sterically more demanding valine derived aza-[2,3]-Wittig rearrangement precursor (*S*)-**6b**.

Table 1 Aza-[2,3]-Wittig sigmatropic rearrangement of (*S*)-**6b**

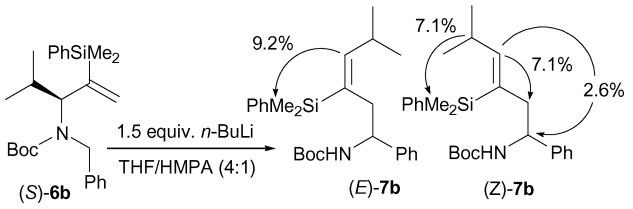
Temp/°C	Time/mins	Yield (%)	*E* : *Z*[a]	Ee (*E*) (%)[b]
−78	10	48	1 : 1	—
−20	5	100[c]	2 : 1	—
0	5	74	3 : 1	58
rt	5	63	4 : 1	56

[a] Determined by ^{1}H NMR. [b] Determined by chiral HPLC.[22] [c] Conversion by ^{1}H NMR.



(3)

Complete conversion of (*S*)-**6b** required 1.5 equiv. of *n*-BuLi, as in the rearrangement of the alanine derived precursor (*S*)-**6a**. Higher yields were obtained at near ambient reaction temperatures, but a non intuitive temperature dependence of the alkene stereoselection was noted (Table 1). The best diastereoselection was achieved by rearrangement at room temperature (4 : 1 *E* : *Z*) in comparison to −78 °C (1 : 1 *E* : *Z*). Differentiation of the alkene stereoisomers was again inferred from selected one dimensional NOE experiments. The enantiomeric excess of (*E*)-**7b** was determined to be 58% from the rearrangement at 0 °C and 56% from the rearrangement at room temperature by chiral HPLC analysis.[22] The absolute stereochemistry was not determined due to the moderate enantioselectivity.



(4)

The stereoselection from the rearrangements of (*S*)-**6a,b** (eqns. (3,4)) can be rationalised by analysing the proposed transition states for this pericyclic reaction (Fig. 1). Assuming a five membered envelope type transition state then our chiral rearrangement precursors [(*S*)-**6a,b**] can undergo rearrangement through one of four possible transition states to either enantiomer of both the *E* and *Z* alkene product. We expected, in accord with a literature example in the oxy-[2,3]-Wittig series,[23] that the 1,2-interaction between R and $SiMe_2Ph$ in **TS3** and **TS4** would favour **TS1** and **TS2** and hence the *E*-alkene geometry. The degree of chirality transfer would be determined by whether the anion stabilising phenyl substituent chose to adopt an *endo* (**TS2**, **TS3**) or *exo* (**TS1**, **TS4**) orientation in the transition state. Previous work of ours with achiral substrates has shown that the avoidance of the pseudo-1,3-diaxial steric interaction between Ph and $SiMe_2Ph$, such as that present in **TS2** and **TS3**, has dominated stereoselection.[1a] In the present chiral systems, **TS1** and **TS3** also possess destabilising pseudo-1,3-diaxial steric interactions between R and the anion stabilising group Ph. An additional complicating factor that separates this methodology from the oxy-[2,3]-Wittig rearrangement technology is the configurational stability of benzylic anions adjacent to a *N*-Boc dipole. Deprotonation of (*S*)-**6a,b** at temperatures below about −40 °C,[24] assuming that the remote stereocentre at C1 does not impart complete stereocontrol, would give two diastereomeric

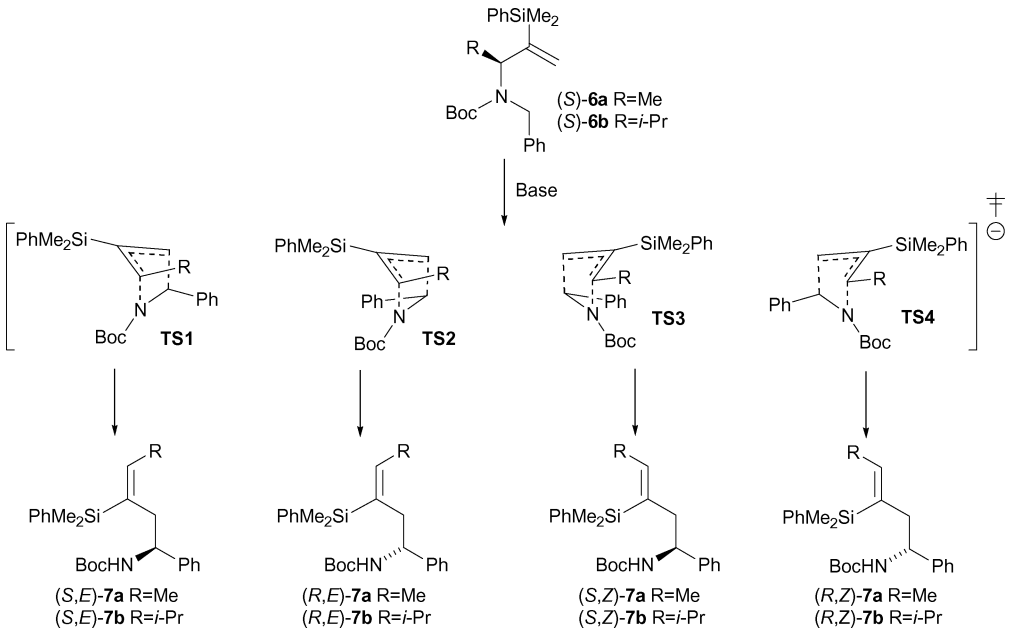
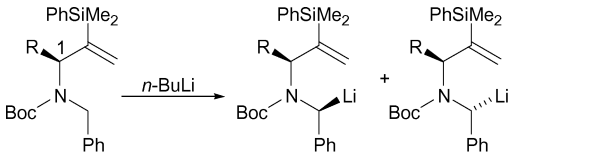


Fig. 1 Proposed possible transition state models for the rearrangement of (*S*)-**6**.

organolithium species (*S*,*S*) and (*S*,*R*)-**8** (eqn. (5)). Accepting that aza-[2,3]-Wittig sigmatropic rearrangements are stereospecific, proceeding with complete inversion of configuration at the lithium-bearing carbanion centre,[25,26] two extreme scenarios are then possible. If rearrangement occurs much faster than racemisation of the lithio carbanion each diastereoisomer will rearrange through separate pairs of transition states that will lead to enantiomeric pairs of products containing either olefin geometry. That is (*S*,*S*)-**8** through **TS2** or **TS4** to give (*R*,*E*) or (*R*,*Z*)-**7** and (*S*,*R*)-**8** through **TS1** or **TS3** to give (*S*,*E*) or (*S*,*Z*)-**7**. For each product enantiomer the *E* : *Z* ratio will depend on the relative destabilising steric interactions in the pairs of transition states. Alternatively if racemisation is much faster than rearrangement then the reaction will proceed through the lowest energy transition state of **TS1**-**4**.

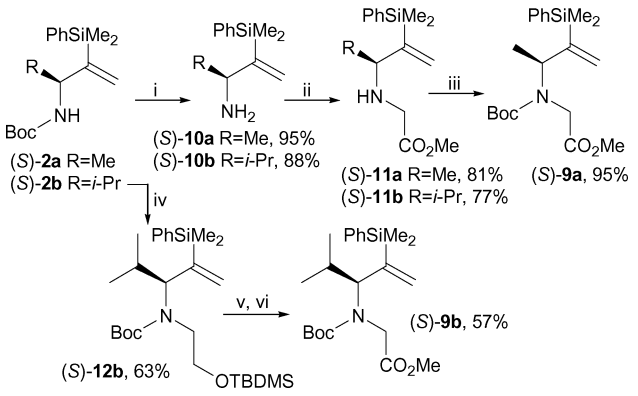


(5)

The low alkene stereoselection observed in the rearrangement of alanine derived precursor (*S*)-**6a** (eqn. (3)) indicates that the methyl group is not large enough to differentiate efficiently between the pairs of transition states **TS1/2** and **TS3/4**. Rearrangement of the valine derived precursor (*S*)-**6b** (eqn. (4)) gave good alkene stereoselection only at near ambient temperatures (Table 1). At these temperatures (specifically 0 °C and rt) racemisation of the lithio carbanion will be rapid and the alkene stereoselection reflects the effectiveness of the isopropyl group to favour the pair of transition states **TS1/2**. The 56–58% enantiomeric excess indicates the similar transition state energies of **TS1** and **TS2**. In order to improve the stereoselection of the process we decided to investigate planar carbanions generated by using an ester as the anion stabilising group. We assumed that the complications arising because of the configuration of the lithio carbanion at low temperatures would be circumvented, such that stereoselection would be dictated by access to any of the four possible transition states at any temperature.

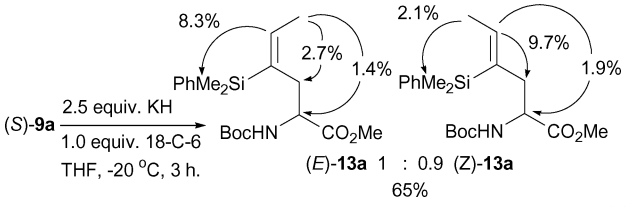
We have already shown that achiral methyl ester aza-[2,3]-rearrangement precursors rearrange with good diastereocontrol.[1b] We hoped to access the desired precursors (*S*)-**9a,b** directly from (*S*)-**2a,b** by alkylation with a suitable electrophile. Direct alkylation of the potassium anion of (*S*)-**2a,b** with methyl bromoacetate or its iodo analogue proved unsuccessful under a variety of conditions. The failure of this reaction was most probably due to deprotonation of the electrophile by the aza anion and led us to investigate the sodium salt of bromo- and iodoacetic acid in an attempt to reduce the acidity of the methylene protons, but both were unsuccessful. A more circuitous route involved removal of the Boc group from (*S*)-**2a,b** to give the amine (*S*)-**10a,b** in good yield (Scheme 3). Mono alkylation with methyl bromoacetate by a literature procedure,[27] with the essential modification of performing the reaction at 0 °C, gave (*S*)-**11a**, and (*S*)-**11b** in 81% and 77% yields respectively. Reprotection with Boc_2O proved very difficult, but under the forcing conditions of Kabalka *et al.*[28] we were able to synthesise (*S*)-**9a** in 95% yield. Surprisingly even under these and even harsher conditions,[29] no product formation was observed for the valine derived secondary amine (*S*)-**10b**. We therefore attempted to alkylate (*S*)-**2b** with commercially available 2-bromoethoxy-*t*-butyldimethylsilane as a two carbon electrophile that contained no acidic protons and appropriate functionality for subsequent elaboration to the required ester. Alkylation required considerable optimisation starting from the conditions we had used to benzylate (*S*)-**2b**. Guided by deuterium quench studies with D_2O we found complete deprotonation of (*S*)-**2b** with KH in DMF required 80 mins at 0 °C. Addition of an electrophile and catalytic TBAI (10 mol%) and stirring for 30 mins at 0 °C then no more than 1 h at room temperature led to a reproducible 63% of (*S*)-**12b**. Selective removal of the silyloxy protecting group was achieved using TBAF (92%) and the free alcohol oxidised to the corresponding acid using Jones' reagent followed by immediate esterification with diazomethane to give (*S*)-**9b** in 57% yield over two steps (Scheme 3). The enantiomers (*R*)-**9a,b** were synthesised in an identical fashion and HPLC analysis confirmed greater than 95% enantiomeric purity.[30]

Rearrangement precursor (*S*)-**9a** was treated with KH/18-C-6 or LDA to initiate aza-[2,3]-rearrangement as we knew from previous studies that the ester function was incompatible with *n*-BuLi. Optimisation of temperature and equivalents of base led to a 65% yield of desired product **13a**, but no improvement in the alkene stereoselectivity of ~1 : 1 by ^{1}H NMR (eqn. (6)).



Scheme 3 *Reagents and conditions*: i, 4 M HCl in dioxane, rt; ii, $BrCH_2CO_2Me$, Et_3N, DMF, 0 °C; iii, Boc_2O, Et_3N, 89 °C; iv, KH, DMF, 0 °C, 80 mins; $BrCH_2CH_2OTBDMS$, TBAI, 0 °C, 30 mins then rt 1 h; v, TBAF, THF, rt, 92%; vi, Jones' reagent, acetone, 0 °C; CH_2N_2, Et_2O, rt 62%.

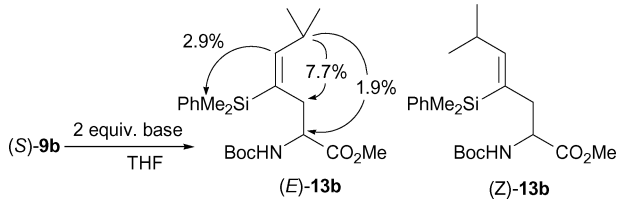
Differentiation of the alkene stereoisomers was again inferred from selected one dimensional NOE experiments.



(6)

Investigation into the use of freshly prepared[31] and titrated[32] KHMDS with 18-C-6 at −40 °C for 6 h did lead to a 1 : 7 *E* : *Z* stereoselectivity, but only in a poor 25% yield. This alkene stereoselection is far greater than when using KH, even though it is the same counter ion. Re-subjecting the product (1 : 7 *E* : *Z*) to the reaction conditions verified that there was no selective destruction of one diastereoisomer. The origin and sense of this increased selectivity remains unclear. The degree of chirality transfer in these reactions was not measured due to either the poor alkene stereoselection and/or the poor yields obtained. This substrate [(*S*)-**9a**] was behaving similarly to the corresponding benzyl substrate [(*S*)-**6a**] and we could again conclude that the stereogenic methyl substituent was, in the majority of reactions, not of sufficient steric bulk to energetically differentiate diastereomeric transition states.

Rearrangement of valine precursor (*S*)-**9b** using the KH/18-C-6 conditions led to the best yield and alkene stereoselection (eqn. (7), Table 2).



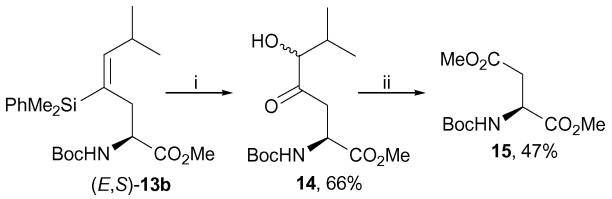
(7)

The use of LDA or KHMDS gave inferior results. The (*E*)-alkene was verified from selected one dimensional NOE experiments. The highest enantiomeric excess of the major product (*E*)-**13b** was determined to be 79% (50% yield) by chiral HPLC.[33] Determination of the absolute stereochemistry of (*E*)-**13b** was achieved by degradation to a known aspartic acid derivative. Treatment of (*E*)-**13b** (70% ee) with ozone and stirring with water overnight gave the ketol **14** in 66% yield (Scheme 4).[34] Cleavage with $NaIO_4$[35] and esterification with diazomethane gave *N*-Boc-L-aspartic acid dimethyl ester (**15**) in 47% yield, $[\alpha]_D$ +20.5 (*c* 0.4, $CHCl_3$), [lit.[36] $[\alpha]_D$ +30.8 (*c* 2.1, $CHCl_3$)].

Table 2 Aza-[2,3]-Wittig sigmatropic rearrangement of (*S*)-**9b**

Base	Temp/°C	Time/h	Yield (%)[a]	*E* : *Z*[b]	Ee (*E*) (%)[c]
KH	0	1	66	10 : 1	70
KH	−20	2	50	10 : 1	79
LDA	−40	16	12	5 : 1	66
LDA	−20	1.5	56	5 : 1	50
KHMDS	−40	6	56	5 : 1	—

[a] Isolated by flash chromatography, yield refers to inseparable (*E*/*Z*)-**13b** mixture. [b] Determined by ^{1}H NMR. [c] Ee of major isomer, determined by chiral HPLC. [d] Reaction in the presence of 20% HMPA instead of 18-C-6.



Scheme 4 *Reagents and conditions*: i, O_3, MeOH–CH_2Cl_2, −78 °C; H_2O, rt, 14 h; ii, $NaIO_4$, MeOH–H_2O, rt; CH_2N_2, Et_2O, rt.

The large and positive value of the observed $[\alpha]_D$ and the literature value show that the major enantiomer of (*E*)-**13b** is the *S*-enantiomer. The optical purity calculated by comparison of the $[\alpha]_D$ values was in good agreement with the ee previously determined by chiral HPLC (67% *op cf* 70% ee). From the determination of the absolute stereochemistry of the major rearrangement product (*E*,*S*)-**13b** we can infer that the rearrangement prefers to pass through transition state structure **TS5** (Fig. 2). In this structure (**TS5**) the bulky silicon group is dictating all stereochemistry by forcing both the methyl ester and isopropyl substituent to be *exo* in spite of the unfavourable 1,3-interaction between them. This controls the rearrangement at 0 °C in 66% yield with a chirality transfer of 85% (70% ee) and 91% *E* alkene selectivity.

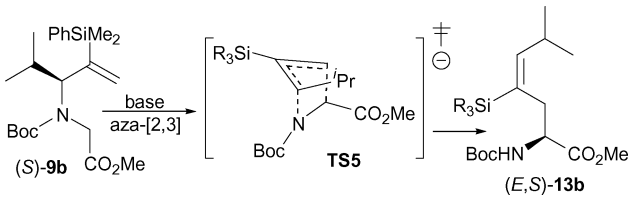
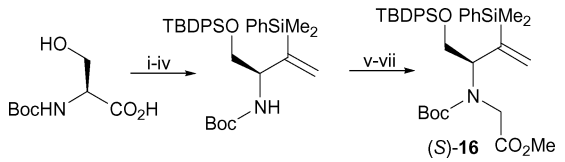


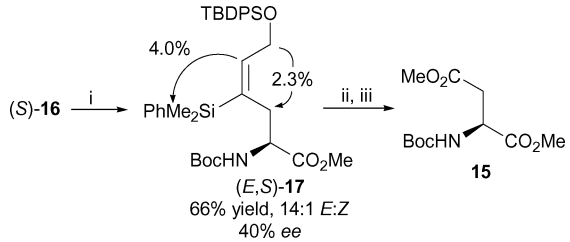
Fig. 2 Favoured transition state structure.

With the successful rearrangement of our valine based models occurring with good transfer of chirality we moved on to look at a more functionalised precursor containing an α-hydroxymethyl substituent that could be derived from serine. We planned that the judicious choice of hydroxyl protecting group would enable the protected α-hydroxymethyl substituent to mimic the effect of the isopropyl group through steric bulk or in some similar way by coordination. The synthesis of serine derived precursor **16** required the use of the bulky TBDPS protecting group for the α-hydroxymethyl substituent and followed the same synthetic sequence as for the synthesis of the alanine precursor **9a** (Scheme 5).[37] The enantiomer (*R*)-**16** was synthesised in an identical fashion and HPLC analysis confirmed greater than 95% enantiomeric purity.[38]

Optimisation of the [2,3]-rearrangement of (*S*)-**16** found the use of an excess of LDA (1.8 equiv.) in THF–HMPA (4 : 1) at 0 °C for 10 mins gave **17** in 14 : 1 *E* : *Z* stereoselectivity in 66% yield (Scheme 6). Use of KH (2 equiv.)/18-C-6 led to complete *E*-alkene stereoselection, but in a lower 36% yield. Prolonged reaction times or lower temperatures led to degradation



Scheme 5 *Reagents and conditions*: i, TBDPSCl, imidazole, DMF, rt; K_2CO_3, MeOH, rt, 94%; ii, CDI, THF, 0 °C, 94%; iii, $(Me_2PhSi)_2CuCNLi_2$, THF, −80 °C, 25%; iv, $Cp_2Ti(CH_2)ClAlMe_2$, THF, −40 °C, 35%; v, TFA–CH_2Cl_2, 0 C, 81%; vi, $BrCH_2CO_2Me$, Et_3N, DMF, 0 °C, 80%; vii, Boc_2O, Et_3N, 89 °C, 93%.



Scheme 6 *Reagents and conditions*: i, 1.8 equiv. LDA, THF–HMPA (4 : 1), 0 °C, 10 mins; ii, O_3, MeOH–CH_2Cl_2, −78 °C; H_2O, rt, 14 h, 64%; ii, $NaIO_4$, MeOH–H_2O, rt; CH_2N_2, Et_2O, rt, 60%.

of product. The (*E*)-alkene was verified from selected one dimensional NOE experiments (Scheme 6). The enantiomeric excess of (*E*)-**17** was determined to be 40% for the material from the LDA rearrangement and 55% for the material from the KH rearrangement by chiral HPLC analysis.[39] Determination of the absolute stereochemistry was achieved in a similar fashion to before by degradation of (*E*)-**17** to *N*-Boc-L-aspartic acid dimethyl ester (**15**, Scheme 6) that was found to have $[a]_D$ +9.3 (*c* 0.3, $CHCl_3$) [lit.[36] $[a]_D$ +30.8 (*c* 2.1, $CHCl_3$)]. The positive $[a]_D$ proves that (*E*)-**17** is the *S*-enantiomer. This result also confirms that the bulky silicon group is again dictating the alkene geometry and the major *S*-stereocentre (**TS6** R = $CH_2OTBDPS$, Fig. 3). The increased preference for formation of the *E*-alkene, but the reduced chirality transfer compared to the valine derived ester (*S*)-**9b** is opposite to what would be expected based on the perceived steric demands of a protected CH_2O–P group *versus* the normally larger iso-Pr substituent. However, these results can be adequately explained if we consider the $CH_2OTBDPS$ group to be sterically larger than the iso-Pr substituent. The larger steric bulk of the substituent attached to the stereogenic centre should increase the *E*-alkene stereoselection by avoiding the destabilising 1,2-interaction with the phenyldimethylsilyl group. Unfortunately the anion stabilising group then has to experience a destabilising 1,3-interaction with the R substituent if *exo* (**TS6** in Fig. 3) or a 1,3-interaction with the phenyldimethylsilyl group if *endo* (**TS7** in Fig. 3). This explains the increased alkene stereoselectivity, but reduced enantioselectivity of (*E*,*S*)-**17**

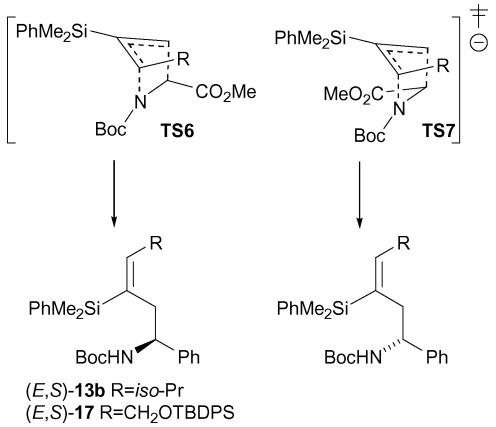


Fig. 3 Competing transition state structures that erode enantioselectivity.

(14 : 1 *E* : *Z*, 40% ee) compared to the valine analogue (*E*,*S*)-**13b** (10 : 1 *E* : *Z*, 79% ee). Ignoring any subtle electronic effects and assuming the OTBDPS group is incapable of coordination to the metal counter ion, it would appear that there is an interplay between the steric bulk of the substituent at the stereogenic centre being large enough to dictate alkene stereoselection, but not so large as to counter too severely the directing effect of the activating phenyldimethylsilyl group, towards the anion stabilising group (CO_2Me in this case).

We envisaged two possible solutions to this problem (Fig. 4). Changing the protecting group of the pendant CH_2OP group from a bulky silane to a more activated group, *e.g.* the MOM group, could enable a positive chelating interaction with the cation associated with the enolate that could only take place when both groups were *exo* (**TS8**). Extrapolating this idea to its extreme convinced us that if the hydroxymethyl group and the ester group could be covalently linked to form a lactone then if rearrangement could occur, the constraints of the system would allow only one transition state structure to be accessed (**TS9**).

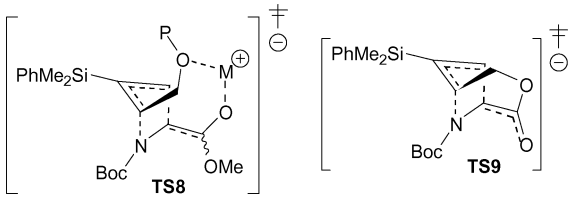
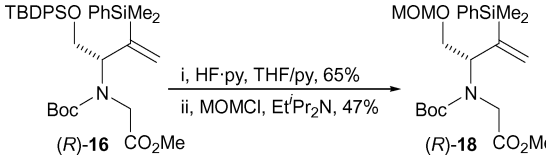


Fig. 4 Transition state models for better enantioselectivity.

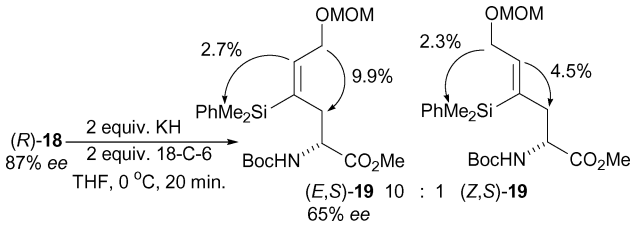
Following a synthetic sequence identical to that used for the preparation of **9b**, but starting from each enantiomer of serine with MOM protection gave a low overall yield for the synthesis of the vinyl silane and the final step oxidation to the ester. This route was left unoptimised as chiral HPLC revealed each enantiomer to have an ee of only 43%.[40] Although not confirmed at present, the most likely points for racemisation are thought to be either the silylcuprate addition step or the initial MOM protection. To rapidly assess the potential of this approach we decided to derivatise the TBDPS protected rearrangement precursor (*R*)-**16** (eqn. (8)). Deprotection of (*R*)-**16** with a HF·pyridine complex gave the desired alcohol in 65% yield. Reprotection with MOMCl and Hunig's base gave the desired precursor (*R*)-**18** in 47% yield. Analysis by chiral HPLC unfortunately revealed the material to be in 87% ee.[39] Although previous batches of either enantiomer of **16** used in the rearrangements (Scheme 6) had previously been shown to be enatiomerically pure,[37] this particular batch had obviously suffered some racemisation during the synthetic sequence to prepare it from *N*-Boc-L-serine (Scheme 5). We think that ageing of the reagents or slight changes in reaction conditions could have led to some epimerisation along the route. Although not ideal, the potential of this approach at this stage could still be assessed using the 87% ee material (*R*)-**18**.



(8)

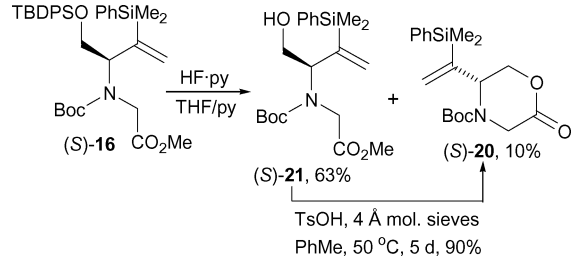
The best aza-[2,3]-rearrangement conditions were found to be using KH/18-C-6 (2 equiv.) in THF at 0 °C for 20 mins. This gave **19** with 10 : 1 *E* : *Z* stereoselectivity in 65% yield (eqn. (9)). Use of LDA (2 equiv.) in THF–HMPA (4 : 1) at 0 °C for 20 mins led to a reduced alkene stereoselection (5 : 1 *E* : *Z*) and a lower 52% yield. Prolonged reaction times or lower temperatures led to product degradation. The (*E*)-alkene geometry was verified from selected one dimensional NOE experiments (eqn. (9)). The sense of enantioinduction was assumed to be identical to the previous

examples (Schemes 4 and 6).[41] The enantiomeric excess of (*E*)-**19** was determined to be 65% by chiral HPLC analysis.[42] As the starting material was in 87% ee this translates to an ee of 75% (corresponding to 88% chirality transfer) if enantiomerically pure (*R*)-**18** had been used. The alkene stereoselectivity is slightly less than when the *O*-silyl protecting group was used, but is still very good. We believe the increased enantioselectivity of this rearrangement (eqn. (9)) supports the potential for chelation to control the stereoselectivity of this type of chirality transfer in the aza-[2,3]-rearrangement. Further studies and refinements are ongoing.



(9)

Synthesis of the cyclic precursor (*S*)-**20** was most easily accomplished by *O*-silyl deprotection of (*S*)-**16** (87% ee) followed by cyclisation. In the event treatment with a HF·pyridine complex gave alcohol (*S*)-**21** with 10% of cyclised (*S*)-**20** (eqn. (10)). After separation by chromatography, the primary alcohol (*S*)-**21** could be treated with TsOH in toluene at 50 °C in the presence of 4 Å molecular sieves for 5 days to give the desired cyclised product (*S*)-**20** in 90% yield. Upon subjection of (*S*)-**20** to a variety of strong bases (KH, LDA, LiTMP) in THF along with 18-C-6 or HMPA, no rearrangement product was observed. The only isolable product which was formed after extended reaction periods at room temperature was the hydroxy acid (47%) caused from direct hydrolysis of (*S*)-**20** by residual water or a hydroxide ion. The hydroxy acid recyclised on standing at room temperature to reform (*S*)-**20**. The reluctance to undergo rearrangement must be attributed to the high energy of the strained bicyclic transition state **TS9** through which the reaction would have to proceed. The high energy of this transition state prevents rearrangement and allows alternative destructive pathways to predominate.



(10)

Summary

The synthesis of enantiomerically pure aza-[2,3]-Wittig rearrangement precursors from amino acids alanine, valine and serine was successful *via* Tebbe methylenation of the corresponding acyl silanes. Potential racemisation of the chiral centre is possible when adjacent to an activated carbonyl function, but can be avoided by the use of fresh silyl cuprate and Tebbe reagent. Rearrangement of phenyl and ester stabilised anions of precursors derived from alanine and valine showed that the activating phenyldimethylsilyl group was able to dictate stereoselectivity effectively only with the larger i-Pr chiral substituent. The ester stabilised anion from the (*S*)-i-Pr series gave a 66% yield with 85% chirality transfer (*S*) and 91% alkene stereoselectivity (*E*). The sense of selectivity could be understood from consideration of transition state models. Development of the more functionalised serine series showed that the *O*-TBDPS serine derivative while efficient at controlling alkene stereoselection (14 : 1, *E* : *Z*), gave a reduced 40% enantioselectivity. By considering transition state models, this was rationalised as the interplay between the bulky *O*-TBDPS group avoiding the vinyl dimethylphenylsilyl substituent, but then causing a detrimental interaction with the anion stabilising group (Fig. 3). Attempts to counteract this by encouraging a positive chelating interaction between a coordinating *O*-MOM serine substituent and the cation associated with the enolate (Fig. 4) led to a 65% yield of rearranged material with 10 : 1 *E* : *Z* alkene stereoselectivity and a chirality transfer equivalent to 88%. This result implies a complimentary coordinating effect or a subtle balance of sterics in the serine derived series. Extrapolation to a covalently bound cyclic precursor [(*S*)-**20**] gave no rearrangement. Further investigations into the steric and possible coordinating interactions of chirality transfer in the aza-[2,3]-Wittig sigmatropic rearrangement and applications to target synthesis will be reported in due course.

Experimental

Our general experimental details have been published.[1b]

[(1*S*)-2-Imidazol-1-yl-1-methyl-2-oxo-ethyl]-carbamic acid *tert*-butyl ester (*S*)-5a

A solution of (*S*)-**4a** (5.00 g, 26.4 mmol) in THF (25 mL) at 0 °C was treated portion wise, over a period of 5 mins with CDI (4.70 g, 29.0 mmol, 1.1 equiv.). After stirring for 30 mins, the reaction was diluted with Et_2O (50 mL) and cautiously quenched with H_2O. The resultant mixture was washed twice with H_2O followed by satd. aq. NaCl before being dried ($MgSO_4$) and concentrated under reduced pressure to furnish the acylimidazole (*S*)-**5a** as a viscous oil which solidified on standing to give a white solid (6.18 g, 98%) and was used directly in the next step. Mp 74–76 °C; $[\alpha]_D$ −9.7 (*c* 2.0, $CHCl_3$); ν_{max}(film)/cm^{-1} 3437, 2978, 2935, 1728, 1714; δ_H (400 MHz; $CDCl_3$) 1.45 (9H, s, ^tBu), 1.52 (3H, d, *J* 7.1, CHCH_3), 4.98 (1H, quin, *J* 7.2, C*H*CH$_3$), 5.23 (1H, bd, *J* 7.0, N*H*), 7.13 (1H, s, CONCH=C*H*), 7.53 (1H, t, *J* 1.5, CONC*H*=CH), 8.27 (1H, s, NC*H*=N); δ_C (100 MHz; $CDCl_3$) 21.3, 30.8, 51.9, 83.4, 118.8, 133.8, 139.0, 157.6, 172.8.

[(1*R*)-2-Imidazol-1-yl-1-methyl-2-oxo-ethyl]-carbamic acid *tert*-butyl ester (*R*)-5a

N-Boc amino acid (*R*)-**4a** (5.00 g, 26.4 mmol) was converted by the procedure above to the corresponding acylimidazole (*R*)-**5a** (5.26 g, 84%) as a viscous oil which solidified on standing to give a white solid. Mp 73–75 °C; $[\alpha]_D$ +9.7 (*c* 2.1, $CHCl_3$). All other data were identical to that for (*S*)-**5a**.

[(1*S*)-2-(Dimethylphenylsilanyl)-1-methyl-2-oxo-ethyl]-carbamic acid *tert*-butyl ester (*S*)-3a

A solution of $PhMe_2SiLi$ (~1 M, 2 equiv.)[13] in THF at 0 °C was added, by syringe over several minutes, to a suspension of CuCN (1.79 g, 20.0 mmol, 1 equiv. dried *in situ* by heating with a heat gun under a steady stream of argon) in THF (60 mL) at 0 °C. The resultant deep red solution was stirred at 0 °C for 20 mins before being cooled to −78 °C and transferred by cannula into a solution of (*S*)-**5a** (4.78 g, 20.0 mmol) in THF (60 mL) at −78 °C. The reaction was stirred for 30 mins before being quenched by the addition of satd. aq. NH_4Cl and warmed to rt. The reaction was opened to the air and vigorously stirred. After 1 hour any solids were removed by filtration and the filtrate was extracted twice with Et_2O. The combined organic extracts were washed with H_2O, followed by satd. aq. NaCl and dried ($MgSO_4$) before being concentrated under reduced pressure. The resulting crude product was purified by flash column chromatography (12% EtOAc–pet. ether) to give the acyl silane (*S*)-**3a** (2.95 g, 48%) as a white solid. Mp 64–65 °C; $[\alpha]_D$ +47.5 (*c* 1.9, $CHCl_3$); ν_{max}(film)/cm^{-1} 3424, 2937, 2932, 1704, 1643; δ_H (400 MHz; $CDCl_3$) 0.53 (3H, s, SiMe_2), 0.53 (3H, s, SiMe_2), 1.08 (3H, d, *J* 7.2, CHCH_3), 1.43 (9H, s, ^tBu), 4.48 (1H, bq, *J* 7.0, C*H*CH$_3$),

5.26 (1H, bs, NH), 7.37–7.43 (3H, m, Ar–H), 7.54–7.57 (2H, m, Ar–H); δ_C (100 MHz; $CDCl_3$) −4.2, −4.2, 16.5, 28.4, 59.8, 79.6, 128.4, 130.2, 134.1, 155.1; *m/z* (ES^+) 308.1681 (4%, MH^+, $C_{16}H_{26}NO_3Si$ requires 308.1682), 174 (100%, $MH_2^+ - SiMe_2Ph$).

[(1*R*)-2-(Dimethylphenylsilanyl)-1-methyl-2-oxo-ethyl]-carbamic acid *tert*-butyl ester (*R*)-3a

Acylimidazole (*R*)-**5a** (2.00 g, 8.37 mmol) was converted by the procedure above to the corresponding acyl silane (*R*)-**3a** (2.95 g, 48%) as a white solid. Mp 64–66 °C; $[\alpha]_D$ −38.4 (*c* 2.2, $CHCl_3$); *m/z* (ES^+) 308.1674 (30%, MH^+, $C_{16}H_{26}NO_3Si$ requires 308.1682). All other data were identical to that for (*S*)-**3a**.

[(1*S*)-2-(Dimethylphenylsilanyl)-1-methylallyl]-carbamic acid *tert*-butyl ester (*S*)-2a

A solution of Tebbe's reagent in PhMe (0.5 M, 50.0 mL, 25.0 mmol, 1.3 equiv.) was added dropwise to a solution of (*S*)-**3a** (6.03 g, 19.6 mmol, 1 equiv.) in THF (100 mL) at −40 °C. The reaction was allowed to stir at −40 °C for 1 h before being diluted with Et_2O (100 mL) and cautiously quenched with 0.1 M NaOH. After gas evolution ceased, the reaction was cautiously allowed to warm to rt with further evolution of gas. Excess solvent was removed under reduced pressure and the residue was taken up in pet. ether. The remaining solid was filtered off and the filtrate concentrated under reduced pressure to give the crude product. Purification by flash column chromatography (10% EtOAc–pet. ether) furnished the desired product (*S*)-**2a** (3.6 g, 60%) as a white solid along with recovered starting material (0.55 g, 9%). Mp 47–49 °C; $[\alpha]_D$ −40.5 (*c* 3.4, $CHCl_3$); ν_{max}(film)/cm^{-1} 3444, 2972, 2931, 1704; δ_H (400 MHz; $CDCl_3$) 0.43 (6H, s, $SiMe_2$), 1.13 (3H, d, *J* 5.9, $CHCH_3$), 1.42 (9H, s, ^tBu), 4.36 (2H, bs, $CHCH_3$, NH), 5.48 (1H, d, *J* 1.8, C=CH_2), 5.84 (1H, dd, *J* 1.6, 0.8, C=CH_2), 7.35–7.37 (3H, m, Ar–H), 7.52–7.55 (2H, m, Ar–H); δ_C (100 MHz; $CDCl_3$) −2.4, 21.5, 28.5, 50.5, 79.1, 125.5, 127.9, 129.2, 133.9, 138.3, 152.4, 155.0; *m/z* (ES^+) 306.1897 (8%, MH^+, $C_{17}H_{28}NO_2Si$ requires 306.1889), 172 (100%, $MH_2^+ - SiMe_2Ph$).

[(1*R*)-2-(Dimethylphenylsilanyl)-1-methylallyl]-carbamic acid *tert*-butyl ester (*R*)-2a

Acyl silane (*R*)-**3a** (200 mg, 0.65 mmol, 1 equiv.) was converted by the procedure above to the corresponding vinyl silane (*R*)-**2a** (127 mg, 64%) as a white solid along with recovered starting material (15 mg, 8%). Mp 46–48 °C; $[\alpha]_D$ +37.9 (*c* 2.0, $CHCl_3$); *m/z* (ES^+) 306.1897 (100%, MH^+, $C_{17}H_{28}NO_2Si$ requires 306.1889). All other data were identical to that for (*S*)-**2a**.

Benzyl-[(1*S*)-2-(dimethylphenylsilanyl)-1-methylallyl]-carbamic acid *tert*-butyl ester (*S*)-6a

A solution of (*S*)-**2a** (1.40 g, 4.60 mmol) in THF (25 mL) was transferred by cannula into a suspension of KH (1.5 equiv. washed twice with pet. ether) in THF (35 mL) at rt. After stirring for 30 mins, BnBr (0.61 mL, 5.1 mmol, 1.1 equiv.) and TBAI (170 mg, 0.46 mmol, 0.10 equiv.) were added and the reaction was left for a further 16 hours before being quenched by the cautious addition of H_2O. The resultant mixture was extracted twice with Et_2O, the combined organics washed with H_2O, satd. aq. NaCl, dried ($MgSO_4$), concentrated under reduced pressure and purified by flash column chromatography (4% EtOAc–pet. ether) to furnish rearrangement precursor (*S*)-**6a** (1.52 g, 84%) as a clear oil. $[\alpha]_D$ −64.0 (*c* 3.0, $CHCl_3$); ν_{max}(film)/cm^{-1} 2960, 2935, 1682; δ_H (400 MHz; $CDCl_3$, 55 °C) 0.44 (6H, s, $SiMe_2$), 1.11 (3H, d, *J* 6.9, $CHCH_3$), 1.41 (9H, s, ^tBu), 3.92 (1H, bd, *J* 16.2, NCH_2), 4.19 (1H, bs, NCH_2), 5.02 (1H, bs, $CHCH_3$), 5.65 (1H, s, C=CH_2), 5.81 (1H, s, C=CH_2), 7.14–7.55 (10H, m, Ar–H); δ_C (100 MHz; $CDCl_3$) −2.9, −2.7, 17.8, 28.4, 41.5, 46.7, 79.6, 126.4, 126.7, 127.4, 127.8, 128.1, 129.1, 138.1, 140.0, 140.6, 150.6, 153.5; *m/z* (CI^+) 396.2356 (16%, MH^+, $C_{24}H_{34}NO_2Si$ requires 396.2359), 262 (100%, $MH_2^+ - SiMe_2Ph$).

Enantiomer (*R*)-**6a** not synthesised as rearrangement of (*S*)-**6a** was unsatisfactory.

[(1*S*)-1-(Imidazole-1-carbonyl)-2-methylpropyl]-carbamic acid *tert*-butyl ester (*S*)-5b

In an identical procedure to the preparation of (*S*)-**5a**, *N*-Boc amino acid (*S*)-**4b** (5.00 g, 23.0 mmol) was converted to its corresponding acylimidazole (*S*)-**5b** (6.02 g, 98%) as a white solid and was used directly in the next step. Mp 82–83 °C; $[\alpha]_D$ +38.4 (*c* 2.0, $CHCl_3$); ν_{max}(film)/cm^{-1} 3445, 3438, 2970, 2934, 1714; δ_H (400 MHz; $CDCl_3$) 0.95 (3H, d, *J* 6.8, $CHCH_3$), 1.04 (3H, d, *J* 6.8, $CHCH_3$), 1.45 (9H, s, ^tBu), 2.17 (1H, oct, *J* 6.6, $CH[CH_3]_2$), 4.79 (1H, dd, *J* 9.0, 5.8, NHCH), 5.24 (1H, d, *J* 9.0, NH), 7.13 (1H, d, *J* 1.0, CONCH=CH), 7.53 (1H, t, *J* 1.6, CONCH=CH), 8.26 (1H, s, NCH=N); δ_C (100 MHz; $CDCl_3$) 17.2, 19.6, 31.5, 58.5, 80.7, 116.3, 131.4, 136.5, 155.7, 169.8.

[(1*R*)-1-(Imidazole-1-carbonyl)-2-methylpropyl]-carbamic acid *tert*-butyl ester (*R*)-5b

In an identical procedure to the preparation of (*S*)-**5a**, *N*-Boc amino acid (*R*)-**4b** (5.00 g, 23.0 mmol) was converted to the corresponding acylimidazole (*R*)-**5b** (5.76 g, 94%) as a white solid. Mp 82–83 °C; $[\alpha]_D$ −38.0 (*c* 2.0, $CHCl_3$). All other data were identical to that for (*S*)-**5b**.

[(1*S*)-1-(Dimethylphenylsilanecarbonyl)-2-methylpropyl]-carbamic acid *tert*-butyl ester (*S*)-3b

In an identical procedure to the preparation of (*S*)-**3a**, acylimidazole (*S*)-**5b** (2.00 g, 7.50 mmol) was converted to its corresponding acyl silane (*S*)-**3b** (1.90 g, 76%) as a pale oil. $[\alpha]_D$ −93.7 (*c* 2.0, $CHCl_3$); ν_{max}(film)/cm^{-1} 3433, 2966, 2932, 1712, 1641; δ_H (400 MHz; $CDCl_3$) 0.47 (3H, d, *J* 6.8, $CHCH_3$), 0.52 (3H, s, $SiMe_2$), 0.54 (3H, s, $SiMe_2$), 0.88 (3H, d, *J* 6.8, $CHCH_3$), 1.43 (9H, s, ^tBu), 2.06–2.14 (1H, m, $CH[CH_3]_2$), 4.48 (1H, dd, *J* 8.6, 2.6, NHCH), 5.07 (1H, d, *J* 8.2, NH), 7.37–7.43 (3H, m, Ar–H), 7.55–7.59 (2H, m, Ar–H); δ_C (100 MHz; $CDCl_3$) −4.4, −4.3, 14.8, 20.3, 28.1, 28.4, 68.5, 79.5, 128.3, 130.1, 133.9, 134.1, 156.0; *m/z* (ES^+) 336.1999 (7%, MH^+, $C_{18}H_{30}NO_3Si$ requires 336.1995), 202 (100%, $MH_2^+ - SiMe_2Ph$).

[(1*R*)-1-(Dimethylphenylsilanecarbonyl)-2-methylpropyl]-carbamic acid *tert*-butyl ester (*R*)-3b

In an identical procedure to the preparation of (*S*)-**3a**, acylimidazole (*R*)-**5b** (6.15 g, 23.0 mmol) was converted to its corresponding acyl silane (*R*)-**3b** (5.30 g, 69%) as a pale oil. $[\alpha]_D$ +93.8 (*c* 2.2, $CHCl_3$); *m/z* (ES^+) 336.1989 (100%, MH^+, $C_{18}H_{30}NO_3Si$ requires 336.1995). All other data were identical to that for (*S*)-**3b**.

[(1*S*)-2-(Dimethylphenylsilanyl)-1-isopropylallyl]-carbamic acid *tert*-butyl ester (*S*)-2b

In an identical procedure to the preparation of (*S*)-**2a**, acyl silane (*S*)-**3b** (1.2 g, 3.58 mmol) was converted to its corresponding vinyl silane (*S*)-**2b** (546 mg, 46%) as a pale oil along with recovered starting material (310 mg, 26%). $[\alpha]_D$ +36.4 (*c* 1.1, $CHCl_3$); ν_{max}(film)/cm^{-1} 3448, 2962, 2930, 1709; δ_H (400 MHz; $CDCl_3$) 0.41 (3H, s, $SiMe_2$), 0.43 (3H, s, $SiMe_2$), 0.72 (3H, d, *J* 6.7, $CHCH_3$), 0.82 (3H, d, *J* 6.8, $CHCH_3$), 1.42 (9H, s, ^tBu), 1.70 (1H, oct, *J* 6.6, $CH[CH_3]_2$), 4.06 (1H, t, *J* 7.3, NHCH), 4.40 (1H, d, *J* 9.0, NH), 5.53 (1H, dd, *J* 2.0, 1.0, C=CH_2), 5.77 (1H, t, *J* 1.6, C=CH_2), 7.34–7.37 (3H, m, Ar–H), 7.52–7.55 (2H, m, Ar–H); δ_C (100 MHz; $CDCl_3$) −2.4, −2.1, 17.1, 20.5, 28.5, 31.1, 60.9, 79.0, 126.6, 127.9, 129.2, 134.0, 138.1, 150.8, 155.5; *m/z* (ES^+) 334.2198 (12%, MH^+, $C_{19}H_{32}NO_2Si$ requires 334.2202), 200 (100%, $MH_2^+ - SiMe_2Ph$).

[(1*R*)-2-(Dimethylphenylsilanyl)-1-isopropylallyl]-carbamic acid *tert*-butyl ester (*R*)-2b

In an identical procedure to the preparation of (*S*)-**2a**, acyl silane (*R*)-**3b** (1.41 g, 4.21 mmol) was converted to its corresponding vinyl silane (*R*)-**2b** (662 mg, 47%) as a pale oil along with recovered starting material (300 mg, 21%). $[a]_D$ −36.8 (*c* 1.1, $CHCl_3$); *m/z* (ES^+) 334.2209 (11%, MH^+, $C_{19}H_{32}NO_2Si$ requires 332.2202), 200 (100%, $MH_2^+ - SiMe_2Ph$). All other data were identical to that for (*S*)-**2b**.

Benzyl-[(1*S*)-2-(dimethylphenylsilanyl)-1-isopropylallyl]-carbamic acid *tert*-butyl ester (*S*)-6b

In an identical procedure to the preparation of (*S*)-**6a**, vinyl silane (*S*)-**2b** (355 mg, 1.02 mmol) was converted to rearrangement precursor (*S*)-**6b** (397 mg, 88%) as a clear oil, in a 1 : 1 ratio of Boc rotamers (>95% ee[21]). $[a]_D$ −107 (*c* 1.3, $CHCl_3$); ν_{max}(film)/cm^{-1} 2960, 2930, 1678; δ_H (500 MHz; $CDCl_3$) 0.33 (1.5H, s, SiMe_2), 0.38 (1.5H, s, SiMe_2), 0.46 (1.5H, s, Si$Me_2)_{rot}$, 0.50 (1.5H, s, Si$Me_2)_{rot}$, 0.72–0.77 (4.5H, m, CHCH_3), 0.84 (1.5H, d, *J* 6.5, CHCH_3), 1.38 (4.5H, s, $^tBu)_{rot}$, 1.51 (4.5H, s, ^tBu), 2.05–2.16 (1H, m, CH[CH_3]$_2$), 4.14 (0.5H, d, *J* 15.9, NC$H_2)_{rot}$, 4.17 (0.5H, d, *J* 15.7, NC$H_2)_{rot}$, 4.26 (0.5H, d, *J* 15.7, NCH_2), 4.30 (0.5H, d, *J* 15.8, NCH_2), 4.47 (0.5H, d, *J* 10.8, NCH), 4.73 (0.5H, d, *J* 11.0, NC$H)_{rot}$, 5.71 (0.5H, s, C=C$H_2)_{rot}$, 5.78 (0.5H, s, C=CH_2), 5.90 (0.5H, s, C=C$H_2)_{rot}$, 5.96 (0.5H, s, C=CH_2), 7.20–7.56 (10H, m, Ar–H); δ_C (125 MHz; $CDCl_3$) −3.6, −3.4, −3.1, 19.3, 19.6, 20.5, 20.8, 27.8, 27.9, 28.4, 28.5, 45.5, 45.9, 61.8, 62.9, 79.6, 79.8, 126.5, 127.7, 127.8, 127.9, 128.1, 129.0, 129.1, 129.3, 129.9, 134.1, 134.2, 137.5, 137.7, 140.0, 140.2, 146.6, 147.5, 156.7, 156.4; *m/z* (CI^+) 424.2672 (13%, MH^+, $C_{26}H_{38}NO_2Si$ requires 424.2640), 324 (100%, MH^+ − Boc).

Benzyl-[(1*R*)-2-(dimethylphenylsilanyl)-1-isopropylallyl]-carbamic acid *tert*-butyl ester (*R*)-6b

In an identical procedure to the preparation of (*S*)-**6a**, vinyl silane (*R*)-**2b** (1.12 g, 3.36 mmol) was converted to rearrangement precursor (*R*)-**6b** (1.23 g, 87%) as a clear oil in a 1 : 1 ratio of Boc rotamers (>95% ee[21]). $[a]_D$ +105 (*c* 2.6, $CHCl_3$); *m/z* (CI^+) 424.2652 (18%, MH^+, $C_{26}H_{38}NO_2Si$ requires 424.2640). All other data were identical to that for (*S*)-**6b**.

1(*R*,*S*)-[3-(Dimethylphenylsilanyl)-1-phenylpent-3-(*Z*,*E*)-enyl]-carbamic acid *tert*-butyl ester 7a

Rearrangement precursor (*S*)-**6a** (100 mg, 0.25 mmol) was dissolved in THF–HMPA (2 mL, 4 : 1) and cooled to −78 °C before being treated with *n*-BuLi (180 μL of a 2.1 M solution in hexanes, 0.38 mmol, 1.5 equiv.). After 15 mins, the bright red solution was quenched by the addition of MeOH and allowed to warm to rt. The reaction was diluted with H_2O (15 mL) and extracted with Et_2O (2 × 15 mL). The combined organics were washed with satd. aq. NaCl (15 mL), dried ($MgSO_4$), concentrated under reduced pressure and purified by flash column chromatography (4% EtOAc–pet. ether) to give **7a** (56 mg, 56%) as a clear oil and an inseparable 1.8 : 1 mixture of *E* and *Z* alkene isomers. $[a]_D$ +0.8 (*c* 2.2, $CHCl_3$); ν_{max}(film)/cm^{-1} 3445, 2956, 2929, 1711; δ_H (500 MHz; $CDCl_3$) 0.35 (5.4H, s, Si$Me_2)_E$, 0.37 (5.4H, s, Si$Me_2)_E$, 0.46 (3H, s, Si$Me_2)_Z$, 0.46 (3H, s, Si$Me_2)_Z$, 1.39 (25.2H, bs, $^tBu)_{E+Z}$, 1.66 (8.4H, ad, *J* 6.7, CHC$H_3)_{E+Z}$, 2.18–2.23 (1H, m, CHC$H_2)_Z$, 2.41–2.44 (1.8H, m, CHC$H_2)_E$, 2.54–2.58 (2.8H, m, CHC$H_2)_{E+Z}$, 4.52–4.75 (5.6H, m, NH, NHC$H)_{E+Z}$, 6.07 (1.8H, q, *J* 6.5, C=C$H)_E$, 6.20 (1H, q, *J* 6.8, C=C$H)_Z$, 6.91–7.56 (28H, m, Ar–$H)_{E+Z}$; δ_C (125 MHz; $CDCl_3$) −2.4, −2.3, −1.2, −0.9, 15.1, 18.4, 28.4, 37.5, 47.2, 54.8, 79.2, 126.0, 126.1, 126.8, 126.9, 127.9, 128.0, 128.4, 128.9, 129.1, 134.0, 134.2, 134.9, 136.4, 138.6, 139.1, 139.8, 142.2, 143.6, 155.2; *m/z* (CI^+) 396.2340 (17%, MH^+, $C_{24}H_{34}NO_2Si$ requires 396.2359), 262 (38%, MH^+ − ^{t}Bu, -Ph), 135 (36%, $SiMe_2Ph^+$), 57 (52%, $^tBu^+$).

[3-(Dimethylphenylsilanyl)-5-methyl-1-phenylhex-3-enyl]-carbamic acid *tert*-butyl ester 7b

Rearrangement precursor (*S*)-**6b** (100 mg, 0.24 mmol) was dissolved in THF–HMPA (2 mL, 4 : 1) and cooled to 0 °C before being treated with *n*-BuLi (170 μL of a 2.1 M solution in hexanes, 0.35 mmol, 1.5 equiv.). After 5 mins, the bright red solution was quenched by the addition of MeOH and allowed to warm to rt. The reaction was diluted with water (15 mL), extracted with Et_2O (2 × 15 mL), the combined organics were washed with satd. aq. NaCl (15 mL), dried ($MgSO_4$), concentrated under reduced pressure and purified by flash column chromatography (5% EtOAc–pet. ether) to give **7b** (74 mg, 74%) as a clear oil and an inseparable 3 : 1 mixture of *E* and *Z* alkene isomers (*E* alkene ee 58%[22]). $[a]_D$ +3.8 (*c* 2.5, $CHCl_3$); ν_{max}(film)/cm^{-1} 3446, 2959, 2932, 1710; δ_H (500 MHz; $CDCl_3$) 0.47 (9H, s, Si$Me_2)_E$, 0.48 (9H, s, Si$Me_2)_E$, 0.53 (3H, s, Si$Me_2)_Z$, 0.54 (3H, s, Si$Me_2)_Z$, 0.85 (3H, d, *J* 6.5, CHC$H_3)_Z$, 0.92 (9H, d, *J* 6.3, CHC$H_3)_E$, 0.95 (3H, d, *J* 6.6, CHC$H_3)_Z$, 1.10 (9H, d, *J* 6.5, CHC$H_3)_E$, 1.49 (36H, bs, $^tBu)_{E+Z}$, 2.30 (1H, dd, *J* 13.5, 10.1, CHC$H_2)_Z$, 2.48–2.52 (4H, m, CHCH_{2E}, CH[CH_3]$_{2,Z}$), 2.59–2.64 (4H, m, CHC$H_2)_{E+Z}$, 2.70–2.80 (3H, m, CH[CH_3]$_2)_E$, 4.46 (4H, bs, NHC$H)_{E+Z}$, 4.74, (3H, bs, N$H)_E$, 4.85, (1H, bs, N$H)_Z$, 5.85 (3H, d, *J* 9.6, C=C$H)_E$, 5.90 (1H, d, *J* 10.5, C=C$H)_Z$, 7.15–7.65 (40H, m, Ar–$H)_{E+Z}$; δ_C (125 MHz; $CDCl_3$) −2.2, −2.1, −0.9, −0.6, 22.3, 22.7, 22.8, 28.0, 28.4, 31.5, 38.0, 46.7, 54.8, 79.1, 126.0, 126.1, 126.9, 127.9, 128.4, 128.9, 129.0, 130.7, 131.8, 134.0, 134.2, 138.7, 139.4, 143.8, 153.0, 155.1, 155.8; *m/z* (FAB) 424.2669 (3%, MH^+, $C_{26}H_{37}NO_2Si$ requires 424.2672), 135 (100%, $SiMe_2Ph^+$), 57 (56%, $^tBu^+$).

In an identical fashion (*R*)-**6b** (94 mg, 0.22 mmol) was rearranged to give **7b** (63 mg, 67%) as an inseparable, mixture of alkene isomers in an *E* : *Z* ratio of 3 : 1 (*E* alkene ee 58%[22]). $[a]_D$ +1.5 (*c* 2.5, $CHCl_3$); *m/z* (FAB) 424.2659 (7%, MH^+, $C_{26}H_{37}NO_2Si$ requires 424.2672). All other data were identical to that shown above.

(1*S*)-2-(Dimethylphenylsilanyl)-1-methylallylamine (*S*)-10a

The Boc protected amine (*S*)-**2a** (1.20 g, 3.93 mmol) was treated with a solution of HCl in dioxane (4 M, 3.93 mL, 15.7 mmol, 4 equiv.), and stirred at rt for 1.5 hours. The reaction was diluted with H_2O (20 mL) and washed with Et_2O (20 mL), the organic portion was back extracted with H_2O (20 mL) and the combined aqueous phases were basified with satd. aq. $NaHCO_3$ solution. The basified aqueous phase was extracted with Et_2O (2 × 25 mL), the organic phases combined, washed with brine (50 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give (*S*)-**10a** (767 mg, 95%) as a pale oil, with no further purification necessary. $[a]_D$ −2.6 (*c* 3.4, $CHCl_3$); ν_{max}(film)/cm^{-1} 3374, 2954; δ_H (400 MHz; $CDCl_3$) 0.43 (3H, s, SiMe_2), 0.44 (3H, s, SiMe_2), 1.11 (3H, d, *J* 6.7, CHCH_3), 2.06 (2H, bs, NH), 3.64 (1H, q, *J* 6.6, CHCH$_3$), 5.45 (1H, dd, *J* 2.3, 0.8, C=CH_2), 5.91 (1H, dd, *J* 2.3, 1.5, C=CH_2), 7.34–7.37 (3H, m, Ar–H), 7.53–7.56 (2H, m, Ar–H); δ_C (100 MHz; $CDCl_3$) −2.1, −1.9, 24.6, 51.6, 123.9, 127.9, 129.1, 134.0, 138.7, 156.6. *m/z* (ES^+) 206.1369 (24%, MH^+, $C_{13}H_{19}NSi$ requires 206.1365), 128 (100%, M^+ − Ph).

(1*R*)-2-(Dimethylphenylsilanyl)-1-methylallylamine (*R*)-10a

The Boc protected amine (*R*)-**2a** (409 mg, 1.34 mmol) was converted by the procedure above to its corresponding primary amine (*R*)-**10a** (258 mg, 94%) as a pale oil, with no further purification necessary. $[a]_D$ +2.8 (*c* 2.2, $CHCl_3$); *m/z* (ES^+) 206.1362 (24%, MH^+, $C_{13}H_{19}NSi$ requires 206.1365). All other data were identical to that for (*S*)-**10a**.

[(1*S*)-2-(Dimethylphenylsilanyl)-1-methylallylamino]-acetic acid methyl ester (*S*)-11a

Primary amine (*S*)-**10a** (767 mg, 3.74 mmol) was dissolved in DMF (11 mL) and cooled to 0 °C before being treated with Et_3N (626 μl, 4.49 mmol, 1.2 equiv.) followed by methyl bromoacetate (425 μl, 4.49 mmol, 1.2 equiv.). The reaction was allowed to stir at 0 °C for 75 mins before being diluted with EtOAc and washed three times with H_2O, followed by satd. aq. NaCl. The resulting solution was dried ($MgSO_4$), concentrated under reduced pressure and purified by flash column chromatography (20% EtOAc–pet. ether) to give (*S*)-**11a** as a clear oil (834 mg, 81%). $[a]_D$ −16.8 (*c* 3.0, $CHCl_3$); ν_{max}(film)/cm^{-1} 3340, 2954, 1738; δ_H (400 MHz; $CDCl_3$) 0.42 (3H, s, Si*Me*$_2$), 0.43 (3H, s, Si*Me*$_2$), 1.10 (3H, d, *J* 6.6, CHC*H*$_3$), 3.12 (1H, d, *J* 17.5, NHC*H*$_2$), 3.20 (1H, d, *J* 17.4, NHC*H*$_2$), 3.33 (1H, q, *J* 6.6, C*H*CH$_3$), 3.67 (3H, s, O*Me*), 5.50 (1H, d, *J* 2.6, C=C*H*$_2$), 5.88 (1H, dd, *J* 2.6, 1.0, C=C*H*$_2$), 7.33–7.36 (3H, m, Ar–*H*), 7.52–7.54 (2H, m, Ar–*H*); δ_C (100 MHz; $CDCl_3$) −2.2, −2.1, 23.0, 48.6, 51.7, 58.5, 126.4, 127.8, 129.0, 134.0, 138.5, 153.6, 173.2; *m*/*z* (ES$^+$) 278.1573 (62%, MH$^+$, $C_{15}H_{24}NO_2Si$ requires 278.1576).

[(1*R*)-2-(Dimethylphenylsilanyl)-1-methylallylamino]-acetic acid methyl ester (*R*)-11a

The primary amine (*R*)-**10a** (223 mg, 1.09 mmol) was converted by the procedure above to (*R*)-**11a** (277 mg, 92%) as a clear oil, without need for further purification. $[a]_D$ +16.8 (*c* 3.2, $CHCl_3$); *m*/*z* (ES$^+$) 278.1574 (62%, MH$^+$, $C_{15}H_{24}NO_2Si$ requires 278.1576). All other data were identical to that for (*S*)-**11a**.

{*tert*-Butoxycarbonyl-[(1*S*)-2-(dimethylphenylsilanyl)-1-methylallyl]-amino}-acetic acid methyl ester (*S*)-9a

A solution of (*S*)-**11a** (447 mg, 1.61 mmol) in Et_3N (8 mL) was treated with Boc anhydride (423 mg, 1.94 mmol, 1.2 equiv.) and heated to reflux for 4 h. The reaction was allowed to cool to rt, the solvent removed under reduced pressure and the residue purified by flash column chromatography (10% EtOAc–pet. ether) to give (*S*)-**9a** (579 mg, 95%) as a clear oil in a 2 : 1 mixture of Boc rotamers (>95% ee[30]). $[a]_D$ −42.1 (*c* 1.7, $CHCl_3$); ν_{max}(film)/cm^{-1} 2954, 1753, 1691; δ_H (400 MHz; $CDCl_3$) 0.39–0.42 (6H, m, Si*Me*$_2$), 1.17–1.19 (3H, m, CHC*H*$_3$), 1.40 (6H, s, ^{t}*Bu*), 1.44 (3H, s, ^{t}*Bu*)$_{rot}$, 3.13 (0.66H, d, *J* 18.0, NC*H*$_2$), 3.19 (0.66H, d, *J* 18.0, NC*H*$_2$), 3.31 (0.33H, d, *J* 17.6, NC*H*$_2$)$_{rot}$, 3.63 (0.33H, d, *J* 17.6, NC*H*$_2$)$_{rot}$, 3.65 (2H, s, O*Me*), 3.67 (1H, s, O*Me*)$_{rot}$, 4.87 (0.33H, q, *J* 6.5, C*H*CH$_3$)$_{rot}$, 5.11 (0.66H, q, *J* 6.8, C*H*CH$_3$), 5.61–5.64 (1H, m, C=C*H*$_2$), 5.77–5.79 (1H, m, C=C*H*$_2$), 7.34–7.36 (3H, m, Ar–*H*), 7.46–7.49 (2H, m, Ar–*H*); δ_C (100 MHz; $CDCl_3$) −3.6, −2.7, 16.1, 17.0, 28.3, 28.4, 44.1, 51.7, 51.8, 52.3, 54.0, 80.0, 80.4, 127.6, 127.8, 127.9, 129.0, 129.2, 133.8, 137.7, 138.0, 150.4, 150.8, 154.6, 155.0, 171.0, 171.3; *m*/*z* (ES$^+$) 400.1931 (100%, MNa$^+$, $C_{20}H_{31}NO_4NaSi$ requires 400.1920), 378 (82%, MH$^+$).

{*tert*-Butoxycarbonyl-[(1*R*)-2-(dimethylphenylsilanyl)-1-methylallyl]-amino}-acetic acid methyl ester (*R*)-9a

Secondary amine (*R*)-**11a** (35 mg, 0.13 mmol) was converted by the procedure above to (*R*)-**9a** (40 mg, 85%) as a clear oil in a 2 : 1 mixture of Boc rotamers (>95% ee[30]). $[a]_D$ +41.5 (*c* 1.0, $CHCl_3$); *m*/*z* (ES$^+$) 378.2113 (100%, MH$^+$, $C_{20}H_{32}NO_4Si$ requires 378.2101). All other data were identical to that for (*S*)-**9a**.

(1*S*)-2-(Dimethylphenylsilanyl)-1-isopropylallylamine (*S*)-10b

In an identical procedure to the preparation of (*S*)-**10a**, except stirring the reaction for 3 h, Boc protected amine (*S*)-**2b** (1.12 g, 3.36 mmol) was converted to (*S*)-**10b** (306 mg, 88%) as a pale oil that required no further purification. $[a]_D$ +14.6 (*c* 2.0, $CHCl_3$); ν_{max}(film)/cm^{-1} 3378, 2956 (C–H); δ_H (400 MHz; $CDCl_3$) 0.41 (3H, s, Si*Me*$_2$), 0.44 (3H, s, Si*Me*$_2$), 0.78 (3H, d, *J* 6.7, CHC*H*$_3$), 0.83 (3H, d, *J* 6.8, CHC*H*$_3$), 1.20 (2H, bs, N*H*$_2$), 1.67 (1H, oct, *J* 6.6, C*H*[CH$_3$]$_2$), 3.21 (1H, d, *J* 6.2, NH$_2$C*H*), 5.52 (1H, dd, *J* 2.5, 0.7, C=C*H*$_2$), 5.84 (1H, dd, *J* 2.5, 1.3, C=C*H*$_2$), 7.34–7.37 (3H, m, Ar–*H*), 7.53–7.56 (2H, m, Ar–*H*); δ_C (100 MHz; $CDCl_3$) −2.1, −1.8, 16.8, 21.0, 32.1, 62.6, 125.9, 127.8, 129.0, 134.0, 138.7, 154.5; *m*/*z* (ES$^+$) 234.1679 (28%, MH$^+$, $C_{14}H_{24}NSi$ requires 234.1678), 156 (100%, M$^+$ − Ph).

(1*R*)-2-(Dimethylphenylsilanyl)-1-isopropylallylamine (*R*)-10b

In an identical procedure to the preparation of (*S*)-**10b** Boc protected amine (*R*)-**2b** (537 mg, 1.61 mmol) was converted to (*R*)-**10b** (312 mg, 83%) as a pale oil that required no further purification. $[a]_D$ −14.4 (*c* 1.9, $CHCl_3$); *m*/*z* (ES$^+$) 234.1685 (24%, MH$^+$, $C_{14}H_{24}NSi$ requires 234.1678). All other data were identical to that for (*S*)-**10b**.

[(1*S*)-2-(Dimethylphenylsilanyl)-1-isopropylallylamino]-acetic acid methyl ester (*S*)-11b

In an identical procedure to the preparation of (*S*)-**11a**, except the reaction was left to stir for 2 hours, primary amine (*S*)-**10b** (275 mg, 1.18 mmol) was converted to (*S*)-**11b** (277 mg, 77%) as a clear oil that required no further purification. $[a]_D$ −20.6 (*c* 3.3, $CHCl_3$); ν_{max}(film)/cm^{-1} 3364, 2954, 1732; δ_H (400 MHz; $CDCl_3$) 0.41 (3H, s, Si*Me*$_2$), 0.43 (3H, s, Si*Me*$_2$), 0.82 (3H, d, *J* 6.8, CHC*H*$_3$), 0.91 (3H, d, *J* 6.8, CHC*H*$_3$), 1.62 (1H, oct, *J* 6.9, C*H*[CH$_3$]$_2$), 1.68 (1H, bs, N*H*), 2.06 (1H, d, *J* 6.5, NHC*H*), 3.04 (1H, d, *J* 17.6, NHC*H*$_2$), 3.15 (1H, d, *J* 17.5, NHC*H*$_2$), 3.65 (3H, s, O*Me*), 5.56 (1H, d, *J* 2.8, C=C*H*$_2$), 5.74 (1H, dd, *J* 2.8, 0.9, C=C*H*$_2$), 7.32–7.35 (3H, m, Ar–*H*), 7.52–7.55 (2H, m, Ar–*H*); δ_C (100 MHz; $CDCl_3$) −2.0, −1.7, 18.5, 21.0, 31.2, 48.8, 51.6, 71.8, 127.7, 128.9, 134.0, 138.9, 151.3, 173.5; *m*/*z* (ES$^+$) 306.1888 (100%, MH$^+$, $C_{17}H_{28}NO_2Si$ requires 306.1889).

[(1*R*)-2-(Dimethylphenylsilanyl)-1-isopropylallylamino]-acetic acid methyl ester (*R*)-11b

Primary amine (*R*)-**10b** (282 mg, 1.21 mmol) was converted by the procedure above to (*R*)-**11b** (277 mg, 77%) as a clear oil that required no further purification. $[a]_D$ +20.1 (*c* 2.8, $CHCl_3$); *m*/*z* (ES$^+$) 306.1902 (100%, MH$^+$, $C_{17}H_{28}NO_2Si$ requires 306.1889). All other data were identical to that for (*S*)-**11b**.

[2-(*tert*-Butyldimethylsilanyloxy)-ethyl]-[(1*S*)-2-(dimethylphenylsilanyl)-1-isopropylallyl]-carbamic acid *tert*-butyl ester (*S*)-12b

A solution of the *N*-Boc protected amine (*S*)-**2b** (1.53 g, 4.60 mmol) in DMF (3 mL) was transferred by cannula into a stirred suspension of KH (2 equiv. of a 30% w/w suspension in mineral oil, washed twice with pet. ether) in DMF (6 mL) at 0 °C. After stirring for 80 mins, $BrCH_2CH_2OTBS$ (506 μL, 2.36 mmol, 2 equiv.) and TBAI (4.4 mg, 0.12 mmol, 0.10 equiv.) were added and the reaction was stirred for a further 30 mins at 0 °C followed by 1 h at rt before being quenched with pH 7 phosphate buffer solution. The resulting mixture was diluted with Et_2O and washed three times with H_2O, followed by satd. aq. NaCl, dried ($MgSO_4$), concentrated under reduced pressure and purified by flash column chromatography (1.5% EtOAc in pet. ether) to give (*S*)-**12b** (1.43 g, 63%) a clear oil as a 0.6 : 0.4 mixture of Boc rotamers with recovered starting material (281 mg, 18%). $[a]_D$ −82.0 (*c* 1.4, $CHCl_3$); ν_{max}(film)/cm^{-1} 2957, 2929, 2885, 2856, 1679; δ_H (500 MHz; $CDCl_3$) 0.03 (6H, s, Si*Me*$_2$^{t}Bu), 0.38 (2.4H, s, Si*Me*$_2$Ph)$_{rot}$, 0.39 (1.8H, s, Si*Me*$_2$Ph), 0.39 (1.8H, s, Si*Me*$_2$Ph), 0.75 (1.2H, d, *J* 6.4, CHC*H*$_3$)$_{rot}$, 0.78 (1.8H, d, *J* 6.4, CHC*H*$_3$), 0.85 (3H, d, *J* 6.5, CHC*H*$_3$), 0.88 (3.6H, s, Si^t*Bu*)$_{rot}$, 0.89 (4.4H, s, Si^t*Bu*), 1.44 (3.6H, s, O^t*Bu*)$_{rot}$, 1.46 (4.4H, s, O^t*Bu*), 2.11–2.44 (1H, m, C*H*[CH$_3$]$_2$), 2.80 (0.6H,

ddd, *J* 15.6, 10.5, 5.2, OCH_2), 2.90 (0.4H, ddd, *J* 14.1, 9.6, 5.2, OCH_2)$_{rot}$, 3.15 (0.6H, ddd, *J* 15.6, 10.4, 5.4, OCH_2), 3.25 (0.4H, ddd, *J* 13.6, 9.5, 5.7, OCH_2)$_{rot}$, 3.40 (0.6H, td, *J* 9.7, 5.2, NCH_2), 3.44 (0.4H, td, *J* 9.3, 5.2, NCH_2)$_{rot}$, 3.54 (0.6H, td, *J* 9.7, 5.5, NCH_2), 3.67 (0.4H, td, *J* 9.3, 5.8, NCH_2)$_{rot}$, 4.31 (0.4H, d, *J* 10.9, NC*H*)$_{rot}$, 4.56 (0.6H, d, *J* 11.0, NC*H*), 5.69 (0.6H, d, *J* 1.3, C=CH_2), 5.74 (0.4H, d, *J* 1.2, C=CH_2)$_{rot}$, 5.90 (0.6H, s, C=CH_2), 5.92 (0.4H, s, C=H_2)$_{rot}$, 7.32–7.36 (3H, m, Ar–*H*), 7.49–7.53 (2H, m, Ar–*H*); δ_C (125 MHz; $CDCl_3$) −5.2, −3.7, −3.5, −3.0, 18.4, 19.1, 19.6, 20.4, 20.6, 26.0, 27.2, 27.5, 28.5, 28.6, 44.0, 44.1, 60.7, 60.8, 61.3, 62.0, 79.3, 79.6, 127.7, 127.8, 128.4, 129.0, 129.2, 134.1, 137.5, 137.7, 146.8, 147.4, 155.6, 156.0; *m*/*z* (FAB) 492.3347 (1%, MH^+, $C_{27}H_{50}NO_3Si_2$ requires 492.3329), 392 (8%, MH^+ − Boc), 135 (58%, $PhMe_2Si^+$).

[2-(*tert*-Butyldimethylsilanyloxy)-ethyl]-[(1*R*)-2-(dimethyl-phenylsilanyl)-1-isopropylallyl]-carbamic acid *tert*-butyl ester (*R*)-12b

N-Boc protected amine (*R*)-**2b** (1.00 g, 3.00 mmol) was converted by the procedure above to (*R*)-**12b** (970 mg, 66%) a clear oil in a 0.6 : 0.4 mixture of Boc rotamers along with recovered starting material (189 mg, 19%). $[\alpha]_D$ +84.3 (*c* 1.3, $CHCl_3$); *m*/*z* (FAB^+): *m*/*z* 492.3329 (6%, MH^+, $C_{27}H_{50}NO_3Si_2$ requires 492.3329). All other data were identical to that for (*S*)-**12b**.

{*tert*-Butoxycarbonyl-[(1*S*)-2-(dimethylphenylsilanyl)-1-iso-propylallyl]-amino}-acetic acid methyl ester (*S*)-9b

A solution of silyl ether (*S*)-**12b** (1.43 g, 2.91 mmol) in THF (30 mL) was treated with TBAF (7.28 mL of a 1 M solution in THF, 7.28 mmol, 2.5 equiv.). The reaction was stirred at rt for 30 mins before being quenched by the addition of pH 7 phosphate buffer solution. The reaction was diluted with Et_2O (30 mL), washed with H_2O (30 mL), satd. aq. NaCl (30 mL), dried ($MgSO_4$), concentrated under reduced pressure and purified by flash column chromatography (20% EtOAc–pet. ether) to give the primary alcohol (1.00 g, 92%) as a clear oil in a 0.7 : 0.3 mixture of Boc rotamers. $[\alpha]_D$ −90.0 (*c* 1.8, $CHCl_3$); ν_{max}(film)/cm^{-1} 3624, 3400, 2962, 2930, 1680, 1651; δ_H (400 MHz; $CDCl_3$) 0.40 (2.1H, s, SiMe_2), 0.41 (3.9H, s, SiMe_2), 0.77 (3H, d, *J* 6.4, CHCH_3), 0.87 (0.9H, d, *J* 6.6, CHCH_3)$_{rot}$, 0.89 (2.1H, d, *J* 6.6, CHCH_3), 1.44 (6.3H, s, ^tBu), 1.46 (2.7H, s, O^tBu)$_{rot}$, 2.08–2.16 (1H, m, C*H*[CH_3]$_2$), 2.91 (0.3H, dt, *J* 14.4, 6.5, OCH_2)$_{rot}$, 3.06 (0.7H, ddd, *J* 14.9, 6.3, 3.6, OCH_2), 3.26 (0.3H, dt, *J* 14.5, 6.2, OCH_2)$_{rot}$, 3.34 (0.7H, ddd, *J* 14.9, 6.5, 3.6, OCH_2), 3.51–3.65 (2H, m, NCH_2), 4.34 (0.7H, d, *J* 11.0, NC*H*), 4.59 (0.3H, d, *J* 11.0, NC*H*)$_{rot}$, 5.70 (0.3H, d, *J* 1.6, C=CH_2)$_{rot}$, 5.74 (0.7H, d, *J* 1.7, C=CH_2), 5.85 (0.7H, s, C=CH_2), 5.86 (0.3H, s, C=CH_2)$_{rot}$, 7.33–7.37 (3H, m, Ar–*H*), 7.48–7.51 (2H, m, Ar–*H*); δ_C (100 MHz; $CDCl_3$) −3.7, −3.6, −3.5, −3.0, 19.0, 20.3, 20.5, 21.1, 27.3, 27.6, 28.4, 28.5, 44.4, 44.7, 61.1, 62.3, 63.9, 80.0, 80.8, 127.8, 128.5, 129.0, 129.3, 129.3, 134.1, 137.3, 137.5, 146.9, 148.0, 155.9, 158.3; *m*/*z* (FAB^+) 378.2429 (2%, MH^+, $C_{21}H_{36}NO_3Si$ requires 378.2464), 135 (35%, $PhMe_2Si^+$), 57 (100%, $^tBu^+$).

A solution of the primary alcohol from above (309 mg, 0.820 mmol, 1 equiv.) in acetone (9 mL) was cooled to 0 °C, and treated with Jones' reagent (1.03 mL). The reaction was stirred at 0 °C for 10 mins before being diluted with H_2O (30 mL) and extracted with Et_2O (2 × 30 mL). The combined organics were washed with H_2O (2 × 20 mL) followed by satd. aq. NaCl (20 mL) before being dried ($MgSO_4$) and concentrated under reduced pressure. The crude acid thus obtained was dissolved in Et_2O (10 mL) and CH_2N_2 was bubbled through the solution under a stream of N_2 until a yellow colouration persisted. Further N_2 was bubbled through the reaction until the yellow colouration dissipated and the excess solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (5% EtOAc–pet. ether) and gave (*S*)-**9b** (200 mg, 62%) as a clear oil in a 0.6 : 0.4 mixture of Boc rotamers (>95% ee[30]). $[\alpha]_D$ −98.0 (*c* 2.6, $CHCl_3$); ν_{max}(film)/cm^{-1} 2956, 2931, 2875, 1785, 1693; δ_H (500 MHz; $CDCl_3$) 0.41 (1.2H, s, SiMe_2)$_{rot}$, 0.42 (1.8H, s, SiMe_2), 0.44 (1.8H, s, SiMe_2), 0.45 (1.2H, s, SiMe_2)$_{rot}$, 0.70 (1.2H, d, *J* 6.6, CHCH_3)$_{rot}$, 0.73 (1.8H, d, *J* 6.5, CHCH_3), 0.95 (1.8H, d, *J* 6.4, CHCH_3), 0.96 (1.2H, d, *J* 6.3, CHCH_3)$_{rot}$, 1.41 (5.4H, s, ^tBu), 1.48 (3.6H, s, ^tBu)$_{rot}$, 1.94–2.05 (1H, m, C*H*[CH_3]$_2$), 3.42 (0.6H, d, *J* 17.5, NCH_2), 3.52 (0.4H, d, *J* 17.3, NCH_2)$_{rot}$, 3.67 (3H, s, O*Me*), 3.73 (0.6H, d, *J* 17.3, NCH_2), 3.87 (0.4H, d, *J* 17.1, NCH_2)$_{rot}$, 4.37 (0.4H, d, *J* 11.0, NC*H*)$_{rot}$, 4.59 (0.6H, d, *J* 11.1, NC*H*), 5.63 (0.6H, d, *J* 1.9, C=CH_2), 5.69 (0.4H, d, *J* 1.5, C=CH_2)$_{rot}$, 5.75 (0.6H, s, C=CH_2), 5.79 (0.4H, s, C=CH_2)$_{rot}$, 7.33–7.36 (3H, m, Ar–*H*), 7.50–7.55 (2H, m, Ar–*H*); δ_C (125 MHz; $CDCl_3$) −3.8, −3.8, −3.6, −3.2, 19.3, 19.8, 20.2, 20.4, 27.6, 27.9, 28.3, 28.44, 43.7, 44.1, 51.6, 51.8, 60.8, 62.1, 80.1, 80.5, 127.7, 127.8, 128.2, 129.0, 129.2, 134.1, 134.2, 137.6, 137.8, 147.1, 147.8, 155.2, 155.5, 170.7, 170.9; *m*/*z* (FAB) 406.2417 (7%, MH^+, $C_{22}H_{36}NO_4Si$ requires 406.2414), 135 (100%, $PhMe_2Si^+$).

{*tert*-Butoxycarbonyl-[(1*R*)-2-(dimethylphenylsilanyl)-1-isopro-pylallyl]-amino}-acetic acid methyl ester (*R*)-9b

Silyl ether (*R*)-**12b** (945 mg, 1.93 mmol) was converted by the procedure above to the primary alcohol (668 mg, 92%) as a clear oil in a 0.7 : 0.3 mixture of Boc rotamers. $[\alpha]_D$ +92.4 (*c* 1.6, $CHCl_3$); *m*/*z* (CI^+) 378.2447 (12%, MH^+, $C_{21}H_{36}NO_3Si$ requires 378.2464). All other data were identical to that for the primary alcohol derived from (*S*)-**12b**.

The primary alcohol from above (643 mg, 1.71 mmol) was converted by the procedure above to give (*R*)-**9b** (256 mg, 38%) as a clear oil in a 0.6 : 0.4 mixture of Boc rotamers (>95% ee[30]) along with recovered starting material (100 mg, 16%). $[\alpha]_D$ +96.2 (*c* 1.2, $CHCl_3$); *m*/*z* (FAB) 406.2419 (7%, MH^+, $C_{22}H_{36}NO_4Si$ requires 406.2414). All other data were identical to that for (*S*)-**9b**.

2-*tert*-Butoxycarbonylamino-4-(dimethylphenylsilanyl)-hex-4-enoic acid methyl ester 13a

A solution of (*S*)-**9a** (150 mg, 0.400 mmol, dried by azeotrope with toluene) in THF (1 mL) was transferred by cannula into a stirred suspension of KH (134 mg of a 30% w/w suspension in mineral oil, washed twice with pet. ether, 1.00 mmol, 2.5 equiv.) in THF (1 mL) at −40 °C. 18-C-6 (106 mg, 0.400 mmol, 1.0 equiv.) was added and the reaction was allowed to stir for 2 h before being allowed to warm to −20 °C and stirred for a further 2.5 h. The reaction was quenched with MeOH, allowed to warm to rt, diluted with H_2O (20 mL) and extracted with Et_2O (2 × 20 mL). The organic extracts were washed with satd. aq. NaCl (20 mL), dried ($MgSO_4$), concentrated under reduced pressure and purified by flash column chromatography (12% EtOAc–pet. ether) to give **13a** (98 mg, 65%) as a clear oil and an inseparable 1 : 0.9–1 mixture of *E* and *Z* alkene isomers. $[\alpha]_D$ +0.4 (*c* 2.3, $CHCl_3$); ν_{max}(film)/cm^{-1} 3443, 2954, 1740, 1713; δ_H (400 MHz; $CDCl_3$) 0.40 (3H, s, SiMe_2)$_E$, 0.41 (3H, s, SiMe_2)$_E$, 0.46 (3H, s, SiMe_2)$_Z$, 0.46 (3H, s, SiMe_2)$_Z$, 1.43 (9H, bs, ^tBu)$_E$, 1.44 (9H, bs, ^tBu)$_Z$, 1.63 (3H, d, *J* 5.6, CHCH_3)$_Z$, 1.76 (3H, d, *J* 6.7, CHCH_3)$_E$, 2.32 (1H, dd, *J* 13.4, 9.0, CHCH_2)$_Z$, 2.50 (1H, dd, *J* 13.3, 9.2, CHCH_2)$_E$, 2.58–2.69 (2 H, m, CHCH_2)$_{E+Z}$, 3.67 (3H, s, O*Me*)$_E$, 3.68 (3H, s, O*Me*)$_Z$, 4.25–4.30 (2H, m, NHC*H*)$_{E+Z}$, 4.75 (1H, bd, *J* 7.9, N*H*)$_E$, 4.85 (1H, bd, *J* 7.8, N*H*)$_Z$, 6.11 (1H, q, *J* 6.5, C=C*H*)$_E$, 6.22 (1H, q, *J* 6.9, C=C*H*)$_Z$, 7.33–7.36 (6H, m, Ar–*H*)$_{E+Z}$, 7.51–7.55 (4H, m, Ar–*H*)$_{E+Z}$; δ_C (100 MHz; $CDCl_3$) −2.6, −2.4, −1.2, 15.1, 18.5, 28.3, 32.2, 41.5, 51.9, 52.1, 53.5, 53.9, 79.6, 127.8, 127.9, 128.9, 129.0, 133.1, 133.8, 134.0, 134.9, 138.3, 138.9, 140.7, 142.9, 155.1, 173.2, 173.3; *m*/*z* (EI^+) 377.2006 (3%, MH^+, $C_{20}H_{31}NO_4Si$ requires 377.2022), 135 (100%, $PhMe_2Si^+$).

(2*S*)-2-*tert*-Butoxycarbonylamino-4-(dimethylphenylsilanyl)-6-methylhept-4-enoic acid methyl ester 13b

A solution of rearrangement precursor (*S*)-**9b** (50 mg, 0.13 mmol, dried by azeotrope with toluene) in THF (1 mL) was transferred by cannula into a stirred suspension of KH (34 mg of a 30% w/w suspension in mineral oil, washed twice with pet. ether, 0.26 mmol, 2 equiv.) in THF (1 mL) at −78 °C. 18-C-6 (110 mg, 0.40 mmol, 1 equiv.) was added and the reaction was allowed to stir at −78 °C for 10 mins, before being allowed to warm to −20 °C and stirred for 2 hours and then warmed to 0 °C and stirred for a further 1 hour. The reaction was quenched with MeOH and allowed to warm to rt before being diluted with Et_2O (20 mL). The reaction mixture was then washed with H_2O (2 × 20 mL), satd. aq. NaCl (20 mL), dried ($MgSO_4$), concentrated under reduced pressure and purified by flash column chromatography (10% EtOAc–pet. ether) to give **13b** (33 mg, 66%) as a clear oil and an inseparable >10 : 1 mixture of *E* and *Z* alkene isomers (*E* alkene ee 70%[33]). $[\alpha]_D$ +8.5 (*c* 1.3, $CHCl_3$); ν_{max}(film)/cm^{-1} 3444, 2959, 2931, 2868, 1741, 1712; δ_H (500 MHz; $CDCl_3$) for *E* alkene 0.40 (6H, s, Si*Me*$_2$), 0.95 (3H, d, *J* 6.7, CHC*H*$_3$), 0.99 (3H, d, *J* 6.5, CHC*H*$_3$), 1.42 (9H, s, ^{t}*Bu*), 248 (1H, dd, *J* 13.6, 9.6, CHC*H*$_2$), 2.55 (1H, dd, *J* 13.6, 5.4, CHC*H*$_2$), 3.67 (3H, s, O*Me*), 4.19–4.25 (2H, m, NHC*H*), 4.70 (1H, d, *J* 7.9, N*H*), 5.78 (1H, d, *J* 9.7, C=C*H*), 7.33–7.36 (3H, m, Ar–*H*), 7.50–7.53 (2H, m, Ar–*H*); δ_C (100 MHz; $CDCl_3$) for *E* alkene −2.3, −2.1, 22.7, 22.8, 27.9, 28.4, 32.6, 52.1, 53.6, 79.7, 127.9, 128.1, 129.0, 130.2, 134.1, 138.6, 154.0, 155.1, 173.4; *m/z* (CI$^+$) 406.2409 (7%, MH$^+$, $C_{22}H_{36}NO_4Si$ requires 406.2414), 272 (100%, MH_2^+ − PhMe$_2$Si), 135 (12%, PhMe$_2$Si$^+$).

In an identical fashion (*R*)-**9b** (50 mg, 0.13 mmol) was rearranged to give **13b** (25 mg, 50%) as a clear oil and an inseparable >10 : 1 mixture of *E* and *Z* alkene isomers (*E* alkene ee 70%[33]). $[\alpha]_D$ −9.2 (*c* 1.2, $CHCl_3$); *m/z* (FAB) 406.2411 (10%, MH$^+$, $C_{22}H_{36}NO_4Si$ requires 406.2414). All other data were identical to that detailed above.

(2*S*, 5*R*,*S*)-2-*tert*-Butoxycarbonylamino-5-hydroxy-6-methyl-4-oxo-heptanoic acid methyl ester 14

Ozone was bubbled through a solution of (*E*,*S*)-**13b** (formed by rearrangement of (*S*)-**9b**) (45 mg, 0.11 mmol) in MeOH–CH_2Cl_2 (4.4 mL, 9 : 1) at −78 °C until a blue colouration persisted; O_2 was then bubbled through the solution to remove the excess ozone until it again became clear. After the reaction had been allowed to warm to rt, H_2O (1 mL) was added. The reaction was stirred at rt for 18 h before being diluted with EtOAc (20 mL) and washed with H_2O (20 mL) followed by satd. aq. NaCl (20 mL). The organic portion was dried ($MgSO_4$), concentrated under reduced pressure and purified by flash column chromatography (30% EtOAc–pet. ether) to give **14** (22 mg, 66%) as a clear oil and a 1 : 1.5 mixture of inseparable diastereoisomers. $[\alpha]_D$ +30.0 (*c* 2.0, $CHCl_3$); ν_{max}(film)/cm^{-1} 3527, 3439, 2971, 2932, 2877, 1714; δ_H (400 MHz; $CDCl_3$) 0.93–0.98 (15H, m, CH[C*H*$_3$]$_2$), 1.44 (22.5H, s, ^{t}*Bu*), 1.97–2.06 (2.5H, m, C*H*[CH$_3$]$_2$), 3.03 (1H, dd, *J* 18.4, 4.4, CHC*H*$_2$)$_{min}$, 3.18 (1.5H, dd, *J* 18.2, 4.0, CHC*H*$_2$)$_{maj}$, 3.37 (1.5H, dd, *J* 18.5, 4.6, CHC*H*$_2$)$_{maj}$, 3.46 (1H, dd, *J* 18.2, 4.0, CHC*H*$_2$)$_{min}$, 3.75 (4.5H, s, O*Me*)$_{maj}$, 3.76 (3H, s, O*Me*)$_{min}$, 4.09 (1.5H, d, *J* 6.5, C*H*OH)$_{maj}$, 4.11 (1H, d, *J* 6.2, C*H*OH)$_{min}$, 4.57–4.61 (2.5H, m, NHC*H*), 5.54–5.58 (2.5H, m, N*H*), 9.23 (1.5H, s, O*H*)$_{maj}$, 9.34 (1H, s, O*H*)$_{min}$; δ_C (100 MHz; $CDCl_3$) 19.3, 26.8, 28.4, 42.0, 42.1, 49.3, 52.8, 62.2, 80.3, 90.3, 90.3, 128.0, 130.1, 132.5, 132.6, 132.7, 135.6, 135.7, 155.7, 172.0, 172.2, 207.4, 207.9. *m/z* (CI$^+$) 304.1747 (6%, MH$^+$, $C_{14}H_{26}NO_6Si$ requires 304.1760), 57 (35%, ^{t}Bu$^+$).

(2*S*)-2-*tert*-Butoxycarbonylamino-succinic acid dimethyl ester 15

A solution of ketol **14** (20 mg, 0.070 mmol) in MeOH (1 mL) was treated with a solution of $NaIO_4$ (140 mg, 0.66 mmol, 10 equiv.) in H_2O (0.5 mL) and stirred at rt for 42 h. The reaction was diluted with H_2O (15 mL) and extracted with EtOAc (3 × 15 mL). The organic extracts were then washed with satd. aq. NaCl (15 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude acid thus obtained was dissolved in Et_2O (5 mL) and CH_2N_2 was bubbled through the solution under a stream of N_2 until a yellow colouration persisted. Further N_2 was bubbled through the reaction to remove the excess CH_2N_2, and the solvent was removed under reduced pressure to furnish the crude product. Purification by flash column chromatography (25% EtOAc–pet. ether) gave **15** (8.1 mg, 47%) as a white solid. Mp 62–64 °C (lit.[36] 60 °C); $[\alpha]_D$ +20.5 (*c* 0.4, $CHCl_3$), lit.[36] +30.8° (*c* 2.1, $CHCl_3$), therefore *op* 67%; (found C, 50.93; H, 7.72; N, 5.31. $C_{11}H_{19}NO_6$ requires C, 50.57; H, 7.33; N, 5.36%.); δ_H (500 MHz; $CDCl_3$) 1.46 (9H, s, ^{t}*Bu*), 2.83 (1H, dd, *J* 16.9, 4.6, C*H*$_2$), 3.01 (1H, dd, *J* 17.0, 4.4, C*H*$_2$), 3.71 (3H, s, O*Me*), 3.77 (3H, s, O*Me*), 4.59 (1H, dt, *J* 8.4, 4.2, C*H*), 5.49 (1H, d, *J* 7.6, N*H*).

{*tert*-Butoxycarbonyl-[(1*S*)-1-(*tert*-butyldiphenylsilanyloxymethyl)-2-(dimethylphenylsilanyl)-allyl]-amino}-acetic acid methyl ester (*S*)-16

A solution of *N*-Boc-L-serine (2.50 g, 12.2 mmol) in DMF (25 mL) was treated with imidazole (2.16 g, 31.7 mmol, 2.6 equiv.) followed by TBDPS–Cl (7.92 mL, 30.5 mmol, 2.5 equiv.) and stirred at rt for 16 h. The reaction mixture was diluted with EtOAc (70 mL), washed with H_2O (3 × 70 mL), followed by satd. aq. NaCl (70 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The viscous oil thus obtained was suspended in MeOH–H_2O (43 mL, 70 : 30), treated with K_2CO_3 (4.24 g, 30.5 mmol, 2.5 equiv.) and stirred at rt for 2 h. The MeOH was removed under reduced pressure and the remaining aqueous portion was acidified to pH 1 with 10% citric acid solution before being extracted with CH_2Cl_2 (3 × 40 mL). The organic phases were dried ($MgSO_4$) and concentrated under reduced pressure to give the crude product. The crude product was dissolved in the minimum quantity of hot EtOAc, diluted to 70 mL with pet. ether and left to recrystallise overnight at rt. Filtration gave *N*–Boc–*O*–BDPS–(*S*)-serine (4.94 g, 94%) as a white crystalline solid. Mp 157–158 °C (lit.[43] 155–156 °C); (found C, 64.87; H, 7.46; N, 3.05. $C_{24}H_{33}NO_5Si$ requires C, 64.98; H, 7.50; N, 3.16%.); δ_H (400 MHz; $CDCl_3$) 1.07 (9H, s, Si^t*Bu*), 1.48 (9H, s, O^t*Bu*), 3.91 (1H, dd, *J* 9.9, 3.3, CHC*H*$_2$), 4.13 (1H, dd, *J* 9.6, 1.8, CHC*H*$_2$), 4.43–4.46 (1H, bm, NHC*H*), 5.37 (1H, d, *J* 8.1, N*H*), 7.41–7.45 (6H, m, Ar–*H*), 7.63–7.66 (4H, m, Ar–*H*).

In an identical procedure to the preparation of (*S*)-**5a**, *N*–Boc–*O*–TBDPS–(*S*)–serine (9.38 g, 21.7 mmol) was converted to its corresponding acylimidazole (10.45 g, quant.) as a viscous oil. $[\alpha]_D$ +9.3 (*c* 3.8, $CHCl_3$); ν_{max}(film)/cm^{-1} 3446, 2932, 2859, 1704; δ_H (400 MHz; $CDCl_3$) 0.96 (9H, s, Si^t*Bu*), 1.45 (9H, s, O^t*Bu*), 3.91–3.99 (2H, m, CHC*H*$_2$), 5.08 (1H, dt, *J* 8.1, 4.0, NHC*H*), 5.57 (1H, bs, N*H*), 7.09 (1H, s, CONCH=C*H*), 7.33–7.49 (11H, m, Ar–*H*, CONC*H*=CH), 8.21 (1H, s, NC*H*=N); δ_C (100 MHz; $CDCl_3$) 19.1, 26.6, 28.3, 52.5, 64.4, 80.8, 116.2, 127.9, 130.1, 132.0, 132.2, 135.3, 135.5, 136.5, 155.1, 168.4.

In an identical procedure to the preparation of (*S*)-**3a**, except that the reaction was maintained at under −80 °C using a CO_2–Et_2O bath, the acylimidazole from above (980 mg, 1.99 mmol) was converted to its corresponding acyl silane (277 mg, 25%) as a pale oil. $[\alpha]_D$ +28.5 (*c* 2.9, $CHCl_3$); ν_{max}(film)/cm^{-1} 3435, 2932, 2859, 1705, 1646; δ_H (400 MHz; $CDCl_3$) 0.48 (3H, s, Si*Me*$_2$Ph), 0.48 (3H, s, Si*Me*$_2$Ph), 0.97 (9H, s, Si^t*Bu*), 1.43 (9H, s, O^t*Bu*), 3.77 (1H, dd, *J* 10.9, 3.2, CHC*H*$_2$), 3.94 (1H, dd, *J* 10.9, 2.9, CHC*H*$_2$), 4.47 (1H, dt, *J* 7.9, 3.0, NHC*H*), 5.53 (1H, d, *J* 7.8, N*H*), 7.33–7.52 (15H, m, Ar–*H*); δ_C (100 MHz; $CDCl_3$) −4.5, −4.1, 19.3, 26.8, 28.4, 62.3, 66.0, 79.5, 127.7, 128.3, 129.8, 130.1, 132.9, 133.1, 133.9, 134.1, 135.7, 155.2. *m/z* (CI$^+$) 562.2836 (5%, MH$^+$, $C_{32}H_{44}NO_4Si_2$ requires 562.2809), 135 (87%, PhMe$_2$Si$^+$), 57 (100%, ^{t}Bu$^+$).

In an identical procedure to the preparation of (*S*)-**2a**, the acyl silane was converted to its corresponding vinyl silane (35% plus 22% starting material) as a clear oil. $[\alpha]_D$ −2.5 (*c* 1.1, $CHCl_3$); ν_{max}(film)/cm^{-1} 3442, 2960, 2932, 2895, 2859, 1709; δ_H (400 MHz; $CDCl_3$) 0.34 (6H, s, Si*Me*$_2$), 1.02 (9H, s, Si*t Bu*), 1.43 (9H, s, O*t Bu*), 3.38 (1H, dd, *J* 10.2, 6.8, CHCH_2), 3.60 (1H, dd, *J* 10.5, 4.5, CHCH_2), 4.41 (1H, bs, NHC*H*), 4.71 (1H, d, *J* 8.3, N*H*), 5.54 (1H, d, *J* 0.8, C=CH_2), 5.86 (1H, s, C=CH_2), 7.25–7.59 (15H, m, Ar–*H*); δ_C (100 MHz; $CDCl_3$) −2.7, −2.5, 19.3, 26.9, 28.5, 56.4, 65.6, 79.0, 127.6, 127.8, 127.9, 129.1, 129.7, 129.8, 133.4, 133.9, 135.7, 137.9, 148.3, 155.3. *m/z* (FAB): 560.3040 (19%, MH$^+$, $C_{33}H_{46}NO_3Si_2$ requires 560.3016), 460 (40%, MH$^+$ − Boc), 135 (100%, PhMe$_2$Si$^+$).

The *N*-Boc protected amine from above (210 mg, 0.375 mmol) in CH_2Cl_2 (1.5 mL) was cooled to 0 °C and treated with TFA (0.5 mL). The reaction was allowed to stir at 0 °C for 30 mins before being quenched by the cautious addition of 10% aq. K_2CO_3. The reaction mixture was then diluted with EtOAc (20 mL), washed with H_2O (20 mL), followed by satd. aq. NaCl (20 mL), dried ($MgSO_4$), concentrated under reduced pressure and purified by flash column chromatography (40% EtOAc–pet. ether) to give the primary amine as a clear oil (140 mg, 81%). $[\alpha]_D$ +3.4 (*c* 1.1, $CHCl_3$); ν_{max}(film)/cm^{-1} 3389, 2932, 2858; δ_H (500 MHz; $CDCl_3$) 0.28 (3H, s, Si*Me*$_2$), 0.31 (3H, s, Si*Me*$_2$), 1.04 (9H, s, *t Bu*), 1.72 (2H, bs, NH_2), 3.29 (1H, t, *J* 9.5, CHCH_2), 3.57 (1H, dd, *J* 10.0, 3.4, CHCH_2), 3.71 (1H, dd, *J* 8.7, 3.2, NH$_2$C*H*), 5.54 (1H, d, *J* 2.2, C=CH_2), 5.98 (1H, s, C=CH_2), 7.29–7.63 (15H, m, Ar–*H*); δ_C (125 MHz; $CDCl_3$) −2.5, −2.3, 19.3, 26.9, 57.3, 68.9, 127.3, 127.7, 127.8, 129.0, 129.7, 133.5, 133.7, 133.9, 135.6, 135.6, 138.2, 150.5; *m/z* (FAB): 460.2530 (28%, MH$^+$, $C_{28}H_{38}NOSi_2$ requires 460.2492), 135 (100%, PhMe$_2$Si$^+$).

In an identical procedure to the preparation of (*S*)-**11a**, the primary amine from above (796 mg, 1.73 mmol) was alkylated with methyl bromoacetate to give the corresponding ester (731 mg, 80%) as a clear oil. $[\alpha]_D$ −17.5 (*c* 1.2, $CHCl_3$); ν_{max}(film)/cm^{-1} 3338, 2954, 2931, 2858, 1738; δ_H (500 MHz; $CDCl_3$) 0.23 (3H, s, Si*Me*$_2$), 0.26 (3H, s, Si*Me*$_2$), 1.04 (9H, s, *t Bu*), 2.45 (1H, bs, N*H*), 3.07 (1H, d, *J* 17.4, NHCH_2), 3.27 (1H, d, *J* 17.2, NHCH_2), 3.37 (1H, t, *J* 10.6, CHCH_2), 3.44–3.47 (2H, m, CHCH_2, NHC*H*), 3.66 (3H, s, O*Me*), 5.55 (1H, d, *J* 2.9, C=CH_2), 6.00 (1H, d, *J* 2.8, C=CH_2), 7.25–7.63 (15H, m, Ar–*H*); δ_C (125 MHz; $CDCl_3$) −2.8, −2.8, 19.2, 26.9, 48.5, 51.6, 64.2, 67.6, 127.7, 129.0, 129.5, 129.7, 129.7, 133.4, 133.6, 133.9, 135.7, 137.9, 148.1, 172.9. *m/z* (FAB): 532.2741 (55%, MH$^+$, $C_{31}H_{42}NO_3Si_2$ requires 532.2703), 135 (100%, PhMe$_2$Si$^+$).

A solution of the ester from above (715 mg, 1.35 mmol) in Et_3N (1.35 mL) was treated with Boc anhydride (461 mg, 2.02 mmol, 1.5 equiv.) and heated to reflux. After 16 h, further Boc anhydride was added (154 mg, 0.670 mmol, 0.5 equiv.) and the reaction was refluxed for a further 24 hours. After this time the reaction was allowed to cool to rt and concentrated under reduced pressure, to give the crude product that was purified by flash column chromatography (6% EtOAc–pet. ether) to give the rearrangement precursor (*S*)-**16** (791 mg, 93%) a clear oil and a 0.6 : 0.4 mixture of Boc rotamers (>95% ee[38]). $[\alpha]_D$ −38.7 (*c* 0.5, $CHCl_3$); ν_{max}(film)/cm^{-1} 2954, 2930, 2857, 1753, 1692; δ_H (400 MHz; $CDCl_3$) 0.39–0.41 (6H, m, Si*Me*$_2$), 1.04 (5.4H, s, Si*t Bu*), 1.06 (3.6H, s, Si*t Bu*)$_{rot}$, 1.39 (3.6H, s, O*t Bu*)$_{rot}$, 1.44 (5.4H, s, O*t Bu*), 3.36 (0.6H, d, *J* 17.5, NCH_2), 3.57–3.65 (1.4H, m, NCH_2), 3.60 (1.2H, s, O*Me*)$_{rot}$, 3.61 (1.8H, s, O*Me*), 3.75–3.81 (2H, m, CHCH_2), 4.94 (0.4H, t, *J* 6.8, NC*H*)$_{rot}$, 5.18 (0.6H, t, *J* 6.7, NC*H*), 5.64 (0.6H, s, C=CH_2), 5.73 (0.4H, s, C=CH_2)$_{rot}$, 5.86 (0.6H, s, C=CH_2), 5.99 (0.4H, s, C=CH_2)$_{rot}$, 7.32–7.66 (15H, m, Ar–*H*); δ_C (100 MHz; $CDCl_3$) −3.3, −3.1, −2.8, 19.2, 19.3, 16.8, 26.9, 28.3, 44.7, 44.9, 51.6, 51.8, 57.5, 58.7, 62.5, 127.7, 127.8, 127.9, 129.0, 129.1, 129.2, 129.6, 129.7, 129.8, 134.9, 135.6, 135.7, 137.6, 137.9, 145.6, 146.4, 154.9, 155.2, 170.6, 171.0; *m/z* (FAB): 632.3234 (8%, MH$^+$, $C_{36}H_{50}NO_5Si_2$ requires 632.3228), 532 (48%, MH$^+$ − Boc), 135 (100%, PhMe$_2$Si$^+$).

{*tert*-Butoxycarbonyl-[(1*R*)-1-(*tert*-butyldiphenylsilanyloxy-methyl)-2-(dimethylphenylsilanyl)-allyl]-amino}-acetic acid methyl ester (*R*)-16

As the enantiomer of the rearrangement precursor was only required for HPLC studies, it was prepared from the *O*-TBDMS vinyl silane (from Tebbe methylenation of the acyl silane derived from *N*-Boc-*O*-TBDMS-(*R*)-serine) by deprotection with TBAF and reprotection with TBDPSCl. The remainder of the synthesis from the *O*-TBDPS vinyl silane was completed as above.

In an identical procedure to the preparation of (*S*)-**5a**, *N*-Boc-*O*-TBS-(*R*)-serine (8.10 g, 25.3 mmol) was converted to its corresponding acylimidazole (7.96 g, 85%) as a viscous oil. $[\alpha]_D$ −8.1 (*c* 1.8, $CHCl_3$); ν_{max}(film)/cm^{-1} 3441, 2930, 2884, 2857 (C–H), 1704; δ_H (500 MHz; $CDCl_3$) −0.05 (3H, s, Si*Me*$_2$), −0.04 (3H, s, Si*Me*$_2$), 0.78 (9H, s, Si*t Bu*), 1.45 (9H, s, O*t Bu*), 3.87 (1H, dd, *J* 9.9, 6.2, CHCH_2), 3.99 (1H, dd, *J* 9.9, 4.3, CHCH_2), 5.00–5.06 (1H, m, NHC*H*), 5.46 (1H, d, *J* 8.2, N*H*), 7.11 (1H, s, CONCH=C*H*), 7.53 (1H, s, CONC*H*=CH), 8.25 (1H, s, NC*H*=N); δ_C (125 MHz; $CDCl_3$) −5.7, −5.4, 18.1, 25.6, 28.3, 55.4, 64.1, 80.9, 116.3, 131.2, 136.7, 155.1, 168.8.

In an identical procedure to the preparation of (*S*)-**3a**, the acylimidazole from above (7.80 g, 21.1 mmol) was converted to its corresponding acyl silane (2.4 g, 26%) as a pale oil. $[\alpha]_D$ −54.2 (*c* 1.7, $CHCl_3$); ν_{max}(film)/cm^{-1} 3430, 2954, 2930, 2885, 2858, 1704, 1645; δ_H (500 MHz; $CDCl_3$) −0.08 (3H, s, Si*Me*$_2$*t*Bu), −0.06 (3H, s, Si*Me*$_2$*t*Bu), 0.50 (3H, s, Si*Me*$_2$Ph), 0.53 (3H, s, Si*Me*$_2$Ph), 0.79 (9H, s, Si*t Bu*), 1.43 (9H, s, O*t Bu*), 3.77 (1H, dd, *J* 10.8, 3.1, CHCH_2), 3.97 (1H, dd, *J* 10.8, 2.6, CHCH_2), 4.38 (1H, dt, *J* 7.3, 3.0, NHC*H*), 5.52 (1H, d, *J* 7.0, N*H*), 7.31–7.43 (3H, m, Ar–*H*), 7.54–7.59 (2H, m, Ar–*H*); δ_C (125 MHz; $CDCl_3$) −5.6, −4.4, −4.0, 18.2, 25.8, 28.4, 61.6, 66.2, 79.5, 128.3, 130.1, 134.1, 155.3, 240.1; *m/z* (FAB) 438.2490 (16%, MH$^+$, $C_{22}H_{40}NO_4Si_2$ requires 438.2496), 338 (32%, MH$^+$ − Boc), 135 (100%, PhMe$_2$Si$^+$).

In an identical procedure to the preparation of (*S*)-**2a**, the acyl silane from above (2.03 g, 4.65 mmol) was converted to its corresponding vinyl silane (810 mg, 40%) as a pale oil along with recovered starting material (297 mg, 15%). $[\alpha]_D$ +9.5 (*c* 1.0, $CHCl_3$); ν_{max}(film)/cm^{-1} 3445 (N–H), 2955, 2930, 2885, 2857, 1707; δ_H (500 MHz; $CDCl_3$) −0.07 (3H, s, Si*Me*$_2$*t*Bu), −0.05 (3H, s, Si*Me*$_2$*t*Bu), 0.42 (3H, s, Si*Me*$_2$Ph), 0.43 (3H, s, Si*Me*$_2$Ph), 0.84 (9H, s, Si*t Bu*), 1.43 (9H, s, O*t Bu*), 3.42–3.47 (1H, m, CHCH_2), 3.55 (1H, dd, *J* 10.3, 4.4, CHCH_2), 4.31 (1H, bs, NHC*H*), 4.74 (1H, bs, N*H*), 5.56 (1H, s, C=CH_2), 5.89 (1H, s, C=CH_2), 7.33–7.37 (3H, m, Ar–*H*), 7.52–7.54 (2H, m, Ar–*H*); δ_C (125 MHz; $CDCl_3$) −5.4, −2.5, −2.3, 18.3, 25.9, 28.5, 56.2, 64.7, 78.2, 127.5, 127.9, 129.2, 134.1, 138.1, 148.4, 155; *m/z* (FAB) 436.2688 (25%, MH$^+$, $C_{23}H_{42}NO_3Si_2$ requires 436.2703), 336 (40%, MH$^+$ − Boc), 135 (100%, PhMe$_2$Si$^+$).

A solution of the vinyl silane above (705 mg, 1.62 mmol) in THF (14 mL) was treated with TBAF (2.43 mL of a 1 M solution in THF, 2.43 mmol, 1.5 equiv.). After stirring for 5 mins, the reaction was quenched by the addition of pH 7 phosphate buffer solution (15 mL). The reaction mixture was washed with H_2O (20 mL), followed by satd. aq. NaCl (20 mL), dried ($MgSO_4$), concentrated under reduced pressure and purified by flash column chromatography (30% EtOAc–pet. ether), which gave the alcohol (515 mg, 99%) as a white solid. Mp 99–101 °C; $[\alpha]_D$ +27.2 (*c* 1.2, $CHCl_3$); (found C, 63.35; H, 8.31; N, 4.43. $C_{17}H_{27}NO_3Si$ requires C, 63.51; H, 8.47; N, 4.36%.); ν_{max}(film)/cm^{-1} 3580, 3440, 2962, 1707; δ_H (500 MHz; $CDCl_3$) 0.46 (3H, s, Si*Me*$_2$), 0.46 (3H, s, Si*Me*$_2$), 1.43 (9H, s, *t Bu*), 2.29 (1H, bs, O*H*), 3.42–3.56 (1H, bm, CHCH_2), 3.51–3.55 (1H, bm, CHCH_2), 4.35–4.39 (1H, bm, NHC*H*), 4.92 (1H, bs, N*H*), 5.64 (1H, s, C=CH_2), 5.91 (1H, s, C=CH_2), 7.34–7.38 (3H, m, Ar–*H*), 7.52–7.54 (2H, m, Ar–*H*); δ_C (125 MHz; $CDCl_3$) −2.9, −2.6, 28.4, 56.6, 65.1, 79.6, 127.7, 128.1, 129.4, 133.8, 137.4, 148.2, 156.0; *m/z* (FAB) 322.1847 (10%, MH$^+$, $C_{17}H_{28}NO_3Si_2$ requires 322.1838), 188 (100%, MH$_2^+$ − PhMe$_2$Si).

A solution of the alcohol above (487 mg, 1.52 mmol) in DMF (5.0 mL) was treated with imidazole (109 mg, 1.60 mmol, 1.05 equiv.) followed by TBDPS–Cl (419 μL, 1.60 mmol, 1.05 equiv.) and allowed to stir at rt for 16 hours. The reaction was then diluted with EtOAc (20 mL), washed with H_2O (3 × 20 mL), followed by satd. aq. NaCl (20 mL), dried ($MgSO_4$), concentrated under reduced pressure and purified by flash column chromatography (4% EtOAc–pet. ether) to give *O*-TBDPS vinyl silane (755 mg, 89%) as a clear oil (1.25 g, 93%). $[\alpha]_D$ +2.5 (*c* 1.1, $CHCl_3$); ν_{max}(film)/cm^{-1} 3442, 2960, 2932, 2895, 2859, 1709; δ_H (400 MHz; $CDCl_3$) 0.34 (6H, s, Si*Me*$_2$), 1.02 (9H, s, Si^t*Bu*), 1.43 (9H, s, O^t*Bu*), 3.38 (1H, dd, *J* 10.2, 6.8, CHC*H*$_2$), 3.60 (1H, dd, *J* 10.5, 4.5, CHC*H*$_2$), 4.41 (1H, bs, NHC*H*), 4.71 (1H, d, *J* 8.3, N*H*), 5.54 (1H, d, *J* 0.8, C=C*H*$_2$), 5.86 (1H, s, C=C*H*$_2$), 7.25–7.59 (15H, m, Ar–*H*); δ_C (100 MHz; $CDCl_3$) −2.7, −2.5, 19.3, 26.9, 28.5, 56.4, 65.6, 79.0, 127.6, 127.8, 127.9, 129.1, 129.7, 129.8, 133.4, 133.9, 135.7, 137.9, 148.3, 155.3; *m/z* (FAB) 560.2989 (4%, MH$^+$, $C_{33}H_{46}NO_3Si_2$ requires 560.3016), 460 (96%, MH$^+$ − Boc), 135 (100%, PhMe$_2$Si$^+$).

Following the procedure used in the synthesis of (*S*)-**16**, *N*-Boc protected *O*-TBDPS vinyl silane from above (730 mg, 1.30 mmol) was converted into its corresponding primary amine (558 mg, 93%) as a clear oil. $[\alpha]_D$ −3.8 (*c* 1.5, $CHCl_3$); *m/z* (CI$^+$) 460.2498 (34%, MH$^+$, $C_{28}H_{38}NOSi_2$ requires 460.2492), 406 (83%, M$^+$ − ^{t}Bu), 135 (92%, PhMe$_2$Si$^+$). All other data were identical to the enantiomer prepared in the synthesis of (*S*)-**16**.

Following the procedure used in the synthesis of (*S*)-**16**, the primary amine from above (556 mg, 1.21 mmol) was alkylated with methyl bromoacetate to give the ester (508 mg, 80%) as a clear oil. $[\alpha]_D$ +16.0 (*c* 1.0, $CHCl_3$); *m/z* (FAB$^+$) 532.2687 (88%, MH$^+$, $C_{31}H_{42}NO_3Si_2$ requires 532.2703), 135 (100%, PhMe$_2$Si$^+$). All other data were identical to the enantiomer prepared in the synthesis of (*S*)-**16**.

Following the procedure used in the synthesis of (*S*)-**16**, the secondary amine from above (490 mg, 0.92 mmol) was Boc protected to give the rearrangement precursor (*R*)-**16** (547 mg, 94%) as a clear oil and a 0.6 : 0.4 mixture of Boc rotamers (>95% ee[38]). $[\alpha]_D$ +34.2 (*c* 1.5, $CHCl_3$). *m/z* (FAB) 632.3221 (7%, MH$^+$, $C_{36}H_{50}NO_5Si_2$ requires 632.3228), 532 (58%, MH$^+$ − Boc), 135 (100%, PhMe$_2$Si$^+$). All other data were identical to that for (*S*)-**16**.

(2*S*)-2-*tert*-Butoxycarbonylamino-6-(*tert*-butyldiphenylsilanyloxy)-4-(dimethylphenylsilanyl)-hex-4-enoic acid methyl ester (*E*,*S*)-17

A solution of rearrangement precursor (*S*)-**16** (50 mg, 0.080 mmol, dried by azeotrope with toluene) in THF–HMPA (1.5 mL, 4 : 1) was cooled to 0 °C before being treated dropwise with LDA (148 μL of a 1 M solution in THF and hexane, 0.144 mmol, 1.8 equiv.). After stirring for 10 mins at 0 °C, the reaction was quenched by pouring into pH 7 phosphate buffer solution (15 mL). The mixture thus obtained was extracted with Et_2O (2 × 15 mL), the combined organics were washed with H_2O (20 mL), followed by satd. aq. NaCl (20 mL), dried ($MgSO_4$) concentrated under reduced pressure and purified by flash column chromatography (7.5% EtOAc–pet. ether) to give (*E*,*S*)-**17** (33 mg, 66%) as a clear oil and an inseparable 14 : 1 mixture of *E* and *Z* alkene isomers (*E* alkene ee 40%[17]). $[\alpha]_D$ +7.2 (*c* 1.2, $CHCl_3$); ν_{max}(film)/cm^{-1} 3436, 2955, 2932, 2859, 1741, 1711; δ_H (400 MHz; $CDCl_3$) *E*-alkene 0.40 (6H, s, Si*Me*$_2$), 1.06 (9H, s, Si^t*Bu*), 1.37 (9H, s, O^t*Bu*), 2.32 (2H, bd, *J* 7.5, NHCHC*H*$_2$), 3.57 (3H, s, O*Me*), 4.10 (1H, q, *J* 7.7, NHC*H*), 4.27 (1H, dd, *J* 13.9, 5.8, C*H*$_2$O), 4.32 (1H, dd, *J* 13.8, 5.6, C*H*$_2$O), 4.81 (1H, d, *J* 7.9, N*H*), 6.12 (1H, t, *J* 5.6, C=C*H*), 7.35–7.68 (15H, m, Ar–*H*); δ_C (100 MHz; $CDCl_3$) *E*-alkene −2.7, −2.6, 19.2, 26.9, 28.4, 32.8, 52.1, 53.4, 61.3, 79.7, 127.8, 127.9, 129.2, 129.8, 133.6, 134.1, 135.7, 137.4, 144.7, 155.1, 173.0; *m/z* (FAB) 632.3257 (4%, MH$^+$, $C_{36}H_{50}NO_5Si_2$ requires 632.3228), 532 (17%, MH$^+$ − Boc), 135 (100%, PhMe$_2$Si$^+$).

In an identical fashion (*R*)-**16** (50 mg, 0.080 mmol) was rearranged to give **17** (24 mg, 58%) as a clear oil and an inseparable 14 : 1 mixture of *E* and *Z* alkene isomers (*E* alkene, ee 40%[39]). $[\alpha]_D$ −6.8 (*c* 2.0, $CHCl_3$); *m/z* (FAB) 632.3248 (2%, MH$^+$, $C_{36}H_{50}NO_5Si_2$ requires 632.3228), 532 (8%, MH$^+$ − Boc), 135 (100%, PhMe$_2$Si$^+$). All other data identical to that described above.

(2*S*)-2-*tert*-Butoxycarbonylamino-succinic acid dimethyl ester 15

In an identical procedure to the preparation of **14**, vinyl silane (*E*,*S*)-**17** (formed by rearrangement of (*S*)-**16**) (41 mg, 0.070 mmol) was converted to its corresponding 1,2-ketol (18 mg, 64%) as a clear oil and a 1 : 1 mixture of inseparable diastereoisomers. $[\alpha]_D$ +4.3 (*c* 1.5, $CHCl_3$); ν_{max}(film)/cm^{-1} 3441, 2932, 2860, 1747, 1714; δ_H (400 MHz; $CDCl_3$) 1.04 (9H s, Si^t*Bu*), 1.05 (9H s, Si^t*Bu*), 1.43 (18H, s, O^t*Bu*), 3.10–3.53 (4H, m, NHCHC*H*$_2$), 3.70 (3H, s, O*Me*), 3.72 (3H, s, O*Me*), 3.95–4.04 (4H, m, C*H*$_2$O), 4.43–4.47 (2H, m, C*H*OH), 4.61–4.65 (2H, m, NHC*H*), 5.47–5.51 (2H, m, N*H*), 7.39–7.46 (6H, m, Ar–*H*), 7.64–7.69 (4H, m, Ar–*H*), 9.10 (2H, s, O*H*); δ_C (100 MHz; $CDCl_3$) 19.3, 26.8, 28.4, 42.0, 42.1, 49.3, 52.8, 62.2, 80.3, 90.3, 128.0, 130.1, 132.5, 132.6, 132.7, 135.6, 135.7, 155.7, 172.0, 172.2, 207.4, 207.9; *m/z* (CI$^+$) 530.2567 (5%, MH$^+$, $C_{28}H_{40}NO_7Si$ requires 530.2574), 430 (26%, MH$^+$ − Boc), 57 (37%, ^{t}Bu$^+$).

In an identical procedure to the preparation of **15**, the 1,2-ketol from above (10 mg, 0.02 mmol) was converted to aspartic acid derivative **15** (3 mg, 60%) as a white solid. Mp 58–60 °C, (lit.[36] 60 °C); $[\alpha]_D$ +9.3 (*c* 0.3, $CHCl_3$), lit.[36] +30.8 (*c* 2.1, $CHCl_3$), therefore *op* 30%; all other data in agreement with previous sample and the literature.[36]

{*tert*-Butoxycarbonyl-[(1*R*)-2-(dimethylphenylsilanyl)-1-methoxymethoxymethylallyl]-amino}-acetic acid methyl ester (*R*)-18

A solution of TBDPS ether (*R*)-**16** (299 mg, 0.470 mmol) in THF (2.0 mL) and pyridine (1.0 mL) was cooled to 0 °C and treated with HF·pyridine (250 μL of a 70% w/w solution, 9.40 mmol, 20 equiv.). The reaction was stirred at 0 °C for 15 mins before being allowed to warm to rt and stirred for an additional 18 hours. The reaction was then diluted with H_2O (10 mL) before being quenched by the addition of satd. aq. $NaHCO_3$ and extracted with EtOAc (2 × 15 mL). The combined organics were washed with satd. aq. $CuSO_4$ (15 mL), dried ($MgSO_4$), concentrated under reduced pressure and purified by flash column chromatography (16% EtOAc–pet. ether), which gave recovered starting material (4 mg, 2%), cyclised product (*R*)-**20** (30 mg, 18%) and the desired alcohol (*R*)-**21** (120 mg, 65%) as a clear oil and a 1 : 1 mixture of Boc rotamers. $[\alpha]_D$ +51.4 (*c* 1.4, $CHCl_3$); ν_{max}(film)/cm^{-1} 3478, 2956, 1737, 1682; δ_H (500 MHz; $CDCl_3$) 0.40 (3H, s, Si*Me*$_2$), 0.41 (1.5H, s, Si*Me*$_2$), 0.44 (1.5H, s, Si*Me*$_2$),1.40 (4.5H, s, ^{t}*Bu*), 1.44 (4.5H, s, ^{t}*Bu*), 3.17 (0.5H, d, *J* 17.8, NC*H*$_2$), 3.22 (0.5H, d, *J* 18.0, NC*H*$_2$), 3.27 (0.5H, d, *J* 17.7, NC*H*$_2$), 3.52 (0.5H, d, *J* 17.7, NC*H*$_2$), 3.54–3.60 (1H, m, CHC*H*$_2$), 3.71 (1.5H, s, O*Me*), 3.73 (1.5H, s, O*Me*), 3.73–3.81 (1.5H, m, CHC*H*$_2$, O*H*), 4.02 (0.5H, dd, *J* 11.0, 3.4, CHC*H*$_2$), 4.90–4.93 (0.5H, m, NC*H*), 5.07–5.10 (0.5H, m, NC*H*), 5.64 (0.5H, t, *J* 1.3, C=C*H*$_2$), 5.65 (0.5H, t, *J* 1.3, C=C*H*$_2$), 5.69 (0.5H, t, *J* 1.4, C=C*H*$_2$), 5.70 (0.5H, t, *J* 1.4, C=C*H*$_2$), 7.34–7.38 (3H, m, Ar–*H*), 7.45–7.48 (2H, m, Ar–*H*); δ_C (125 MHz; $CDCl_3$) −3.8, −3.2, −3.0, 28.2, 28.2, 43.9, 44.4, 52.5, 52.7, 58.0, 59.3, 61.5, 80.6, 81.2, 127.9, 128.0, 128.3, 128.5, 129.2, 129.4, 133.8, 137.0, 137.5, 147.7, 148.0, 155.0, 155.7, 173.8, 173.8; *m/z* (CI$^+$): 394.2038 (17%, MH$^+$, $C_{20}H_{32}NO_5Si$ requires 394.2050), 294 (35%, MH$^+$ − Boc), 262 (100%, MH$^+$ − Boc, -MeOH).

A solution of the primary alcohol (*R*)-**21** from above (120 mg, 0.310 mmol) in CH_2Cl_2 (0.9 mL) was treated with Hunig's base (211 μL, 1.22 mmol, 4 equiv.) followed by MOM–Cl (93 μL,

1.2 mmol, 4 equiv.) The reaction was stirred at rt for 3 h before the reaction was quenched with H_2O and extracted with CH_2Cl_2 (2 × 15 mL). The combined organics were washed with satd. aq. NaCl, dried ($MgSO_4$), concentrated under reduced pressure and purified by flash column chromatography (15% EtOAc–pet. ether) to give the rearrangement precursor (*R*)-**18** (63 mg, 47%) as a clear oil and a 0.6 : 0.4 mixture of Boc rotamers (87% ee[40]). $[a]_D$ +37.6 (*c* 2.0, $CHCl_3$); ν_{max}(film)/cm^{-1} 2953, 1754, 1694; δ_H (400 MHz; $CDCl_3$) 0.42 (3H, s, SiMe_2), 0.43 (3H, s, SiMe_2), 1.41 (5.4H, s, ^tBu), 1.44 (3.6H, s, $^tBu)_{rot}$, 3.22 (0.6H, d, *J* 17.7, NCH_2), 3.30 (1.2H, s, CHO$Me)_{rot}$, 3.32 (1.8H, s, CHOMe), 3.42 (0.6H, d, *J* 17.8, NCH_2), 3.54 (0.4H, d, *J* 17.4, NC$H_2)_{rot}$, 3.62 (0.4H, d, *J* 17.4, NC$H_2)_{rot}$, 3.64 (1.8H, s, CO_2Me), 3.66 (1.2H, s, $CO_2Me)_{rot}$, 3.70–3.78 (2H, m, CHCH_2), 4.48–4.53 (2H, m, OCH_2O), 4.92 (0.4H, t, *J* 6.0, NC$H)_{rot}$, 5.13 (0.6H, t, *J* 5.6, NCH), 5.75 (1H, s, C=CH_2), 5.93 (0.4H, s, C=C$H_2)_{rot}$, 5.97 (0.6H, s, C=CH_2), 7.32–7.40 (3H, m, Ar–*H*), 7.48–7.52 (2H, m, Ar–*H*); δ_C (100 MHz; $CDCl_3$) −3.6, −2.9, 28.3, 28.3, 44.9, 45.4, 51.7, 51.9, 55.6, 55.7, 55.8, 57.2, 67.1, 67.4, 80.3, 80.7, 96.7, 97.0, 127.9, 128.0, 129.1, 129.3, 133.9, 137.4, 137.8, 146.6, 147.1, 154.8, 155.1, 170.8, 171.1; *m*/*z* (CI$^+$) 438.2297 (6%, MH$^+$, $C_{22}H_{36}NO_6Si$ requires 438.2312), 338 (13%, MH$^+$ − Boc), 135 (13%, $SiMe_2Ph^+$), 57 (17%, $^tBu^+$).

(2*R*)-2-*tert*-Butoxycarbonylamino-4-(dimethylphenylsilanyl)-6-methoxymethoxyhex-4-enoic acid methyl ester (*E*,*S*)-19

A solution of rearrangement precursor (*R*)-**18** (17 mg, 0.040 mmol, 87% ee,[40] dried by azeotrope with toluene) and 18-C-6 (23 mg, 0.090 mmol, 2 equiv.) in THF (0.4 mL) was cooled to 0 °C before being transferred by cannula into a stirred suspension of KH (12 mg of a 30% w/w suspension in mineral oil, washed twice with pet. ether, 0.090 mmol, 2 equiv.) in THF (0.4 mL). After stirring for 20 mins at 0 °C, the reaction was quenched by pouring into pH 7 phosphate buffer solution (15 mL). The mixture thus obtained was extracted with Et_2O (2 × 15 mL), the combined organics were washed with satd. aq. NaCl (20 mL), dried ($MgSO_4$), concentrated under reduced pressure and purified by flash column chromatography (10% EtOAc–pet. ether) to give (*E*,*S*)-**19** (10 mg, 59%) as a clear oil and an inseparable 10 : 1 mixture of *E* and *Z* alkene isomers (*E* alkene ee 65%[42]). $[a]_D$ −3.4 (*c* 2.1, $CHCl_3$); ν_{max}(film)/cm^{-1} 3440, 2932, 1743, 1713; δ_H (400 MHz; $CDCl_3$) signals for major *E* alkene: 0.44 (6H, s, SiMe_2), 1.42 (9H, s, ^tBu), 2.57 (2H, bd, *J* 8.0, NHCHCH_2), 3.39 (3H, s, CH_2OMe), 3.67 (3H, s, CO_2Me), 4.07–4.24 (3H, m, CHCH_2O, NHCH), 4.66 (2H, s, OCH_2O), 5.34 (1H, d, *J* 7.6, NH), 6.15 (1H, t, *J* 6.2, C=CH), 7.35–7.38 (3H, m, Ar–*H*), 7.45–7.48 (2H, m, Ar–*H*). Signals for minor *Z* alkene: 0.46 (6H, s, SiMe_2), 1.43 (9H, s, ^tBu), 2.37 (1H, dd, *J* 13.1, 8.9, NHCHCH_2), 2.72 (1H, dd, *J* 13.0, 4.4, NHCHCH_2), 3.23 (3H, s, CH_2OMe), 3.69 (3H, s, CO_2Me), 3.92 (2H, d, *J* 6.6, CHCH_2O), 4.26–4.32 (1H, m, NHCH), 4.43 (1H, d, *J* 6.6, OCH_2O), 4.45 (1H, d, *J* 6.6, OCH_2O), 4.88 (1H, d, *J* 8.2, NH), 6.21 (1H, t, *J* 6.6, C=CH), 7.35–7.38 (3H, m, Ar–*H*), 7.45–7.48 (2H, m, Ar–*H*); δ_C (100 MHz; $CDCl_3$) −2.7, −2.5, 28.4, 32.9, 52.2, 53.1, 55.6, 79.6, 96.1, 128.0, 129.3, 134.1, 137.4, 139.9, 140.8, 155.3, 173.2; *m*/*z* (FAB) 460 (15%, MNa$^+$), 438.2337 (2%, MH$^+$, $C_{22}H_{36}NO_6Si$ requires 438.2312), 328 (6%, MH$^+$ − Boc), 135 (31%, $PhMe_2Si^+$), 57 (100%, $^tBu^+$).

(5*S*)-5-[1-(Dimethylphenylsilanyl)-vinyl]-2-oxo-morpholine-4-carboxylic acid *tert*-butyl ester (*S*)-20

In an identical procedure to the preparation of the primary alcohol (*R*)-**21** derived from (*R*)-**16** in the synthesis of (*R*)-**18**, a solution of TBDPS ether (*S*)-**16** (207 mg, 0.340 mmol, 87% ee[38]) gave recovered starting material (*S*)-**16** (33 mg, 16%), cyclised product (*S*)-**20** (12 mg, 10%) and the alcohol (*S*)-**21** (84 mg, 63%) as a clear oil and a 1 : 1 mixture of Boc rotamers. $[a]_D$ −50.1 (*c* 2.2, $CHCl_3$); *m*/*z* (CI$^+$) 394.2038 (17%, MH$^+$, $C_{20}H_{32}NO_5Si$ requires 394.2050). All other data were identical to (*R*)-**21**.

A solution of (*S*)-**21** (115 mg, 0.290 mmol, 1 equiv.) in toluene (3 mL) was treated with TsOH (6 mg, 0.03 mmol, 0.1 equiv.), powdered 4 Å molecular sieves (0.5 g) and the reaction was heated at 50 °C for 64 h. Further TsOH (15 mg, 0.080 mmol, 0.25 equiv.) and powdered 4 Å molecular sieves (0.5 g) were added and the reaction was heated at 50 °C for a further 48 h. The reaction was filtered through a glass sinter and the filtrate was concentrated under reduced pressure to give the crude product that was purified by flash column chromatography (20% EtOAc–pet. ether) to give the rearrangement precursor (*S*)-**20** as a white solid (95 mg, 90%, presumably 87% ee from (*S*)-**16**). Mp 86–88 °C; $[a]_D$ −18.6 (*c* 1.8, $CHCl_3$); ν_{max}(film)/cm^{-1} 2962, 2931, 1755, 1698; δ_H (400 MHz; $CDCl_3$, 55 °C) 0.47 (3H, s, SiMe_2), 0.47 (3H, s, SiMe_2), 1.47 (9H, s, ^tBu), 3.89 (1H, d, *J* 18.3, NCH_2), 4.13 (1H, dd, *J* 11.8, 3.7, OCH_2), 4.23 (1H, dd, *J* 11.9, 3.9, OCH_2), 4.31 (1H, d, *J* 18.3, NCH_2), 4.73 (1H, bs, NCH), 5.71 (1H, t, *J* 1.4, C=CH_2), 5.83 (1H, t, *J* 1.5, C=CH_2), 7.37–7.40 (3H, m, Ar–*H*), 7.51–7.54 (2H, m, Ar–*H*); δ_C (100 MHz; $CDCl_3$) −2.4, 28.4, 44.7, 68.8, 81.4, 128.3, 128.7, 129.7, 134.0, 136.8, 146.0, 153.6, 167.2. *m*/*z* (FAB) 362.1791 (7%, MH$^+$, $C_{19}H_{28}NO_4Si$ requires 362.1788), 135 (46%, $PhMe_2Si^+$), 57 (100%, $^tBu^+$).

{*tert*-Butoxycarbonyl-[(1*S*)-2-(dimethyl-phenyl-silanyl)-1-hydroxymethyl-allyl]-amino}-acetic acid formed from attempted rearrangement of (*S*)-20

A solution of lactone (*S*)-**20** (30 mg, 0.080 mmol, 87% ee, dried by azeotrope with toluene) and 18-C-6 (42 mg, 0.17 mmol, 2 equiv.) in THF (0.8 mL) at 0 °C was transferred by cannula into a stirred suspension of KH (22 mg of a 30% w/w suspension in mineral oil, washed twice with pet. ether, 0.17 mmol, 2 equiv.) at 0 °C. After 30 mins, the reaction was allowed to warm to rt and stirred for a further 1.5 h when TLC indicated only a trace of starting material remaining. The reaction was quenched by pouring into a solution of 10% citric acid (15 mL) and the resultant solution was extracted with Et_2O (2 × 10 mL). The combined organics were washed with satd. aq. NaCl (15 mL), dried ($MgSO_4$), concentrated under reduced pressure and purified by flash column chromatography (EtOAc) to give the corresponding hydroxy acid (15 mg, 48%) as a clear oil and a 0.6 : 0.4 mixture of Boc rotamers which rapidly recyclised on standing at rt to regenerate the starting material (*S*)-**20**. δ_H (400 MHz; $CDCl_3$) 0.39–0.46 (6H, m, SiMe_2), 1.40 (5.4H, s, ^tBu), 1.42 (3.6H, s, $^tBu)_{rot}$, 3.22 (0.6H, d, *J* 14.6, NCH_2), 3.25 (0.6H, d, *J* 17.8, NCH_2), 3.32 (0.4H, d, *J* 17.9, NC$H_2)_{rot}$, 3.58–3.64 (1H, m, CHCH_2), 3.59 (0.4H, d, *J* 17.9, NC$H_2)_{rot}$, 3.75 (0.4H, dd, *J* 12.3, 4.0, CHC$H_2)_{rot}$, 3.83 (0.6H, dd, *J* 12.1, 4.1, CHCH_2), 4.89–4.92 (0.4H, m, NC$H)_{rot}$, 5.05–5.09 (0.6H, m, NCH), 5.65–5.71 (2H, m, C=CH_2), 7.35–7.46 (5H, m, Ar–*H*); δ_C (100 MHz; $CDCl_3$) −3.8, −3.1, −3.0, −2.5, 28.2, 28.3, 43.8, 44.6, 57.4, 59.1, 61.0, 61.2, 81.4, 81.6, 128.0, 128.3, 129.3, 129.4, 133.8, 133.9, 136.9, 137.2, 147.3, 147.5, 155.4, 156.0, 174.8, 175.3. No further data was obtained due to rapid recyclisation to (*S*)-**20**.

Acknowledgements

This work is part of the PhD thesis of MPW. We thank AstraZeneca and the University of Nottingham for funding, Mr T. Spencer for combustion analyses and Mr G. Coxhill and Mr T. Hollingworth for providing mass spectra.

References

1 (*a*) J. C. Anderson, A. Flaherty and M. E. Swarbrick, *J. Org. Chem.*, 2000, **65**, 9152 and references therein; (*b*) J. C. Anderson and S. Skerratt, *J. Chem. Soc., Perkin Trans. 1*, 2002, 2871–9.
2 (*a*) J. C. Anderson and A. Flaherty, *J. Chem. Soc., Perkin Trans. 1*, 2001, 267; (*b*) J. C. Anderson and M. Whiting, *J. Org. Chem.*, 2003, **68**, 6160–3.
3 J. C. Anderson, J. M. A. O'Loughlin and J. A. Tornos, *Org. Biomol. Chem.*, 2005, **3**, 2741.

4 (*a*) K. Mikami, K. Fujimoto, T. Kasuga and T. Nakai, *Tetrahedron Lett.*, 1984, **25**, 6011; (*b*) K. Mikami, O. Takahashi, T. Kasuga and T. Nakai, *Chem. Lett.*, 1985, 1729; (*c*) K. Mikami, K. Fujimoto, T. Kasuga and T. Nakai, *Tetrahedron Lett.*, 1984, **25**, 6011; (*d*) K. Mikami, T. Kasuga, K. Fujimoto and T. Nakai, *Tetrahedron Lett.*, 1986, **27**, 4185; (*e*) O. Takahashi, K. Mikami and T. Nakai, *Chem. Lett.*, 1987, 69; (*f*) E. Nakai and T. Nakai, *Tetrahedron Lett.*, 1988, **29**, 4587; (*g*) R. Brückner, *Chem. Ber.*, 1989, **122**, 193; (*h*) D. Enders, D. Backhaus and J. Runsink, *Angew. Chem., Int. Ed. Engl.*, 1994, **33**, 2098; (*i*) D. Enders and D. Backhaus, *Synlett*, 1995, 631.
5 (*a*) J. A. Marshall and J. Lebreton, *J. Am. Chem. Soc.*, 1988, **110**, 2925; (*b*) J. A. Marshall and X. Wang, *J. Org. Chem.*, 1992, **57**, 2747; (*c*) K. Fujimoto and T. Nakai, *Tetrahedron Lett.*, 1994, **35**, 5019.
6 (*a*) N. Sayo, K. Azuma, K. Mikami and T. Nakai, *Tetrahedron Lett.*, 1984, **25**, 565; (*b*) D. J.-S. Tsai and M. M. Midland, *J. Org. Chem.*, 1984, **49**, 1843; (*c*) N. Sayo, E.-I. Kitahara and T. Nakai, *Chem. Lett.*, 1984, 259.
7 T. Nakai and K. Mikami, *Org. React.*, 1994, **46**, 105.
8 N. Sayo, F. Shirai and T. Nakai, *Chem. Lett.*, 1984, 255.
9 For a review see: A. Ricci and A. Degl'Innocenti, *Synthesis*, 1989, 647.
10 B. F. Bonini, M. Comes-Franchini, G. Mazzanti, U. Passamonti, A. Ricci and P. Zani, *J. Org. Chem.*, 1996, **61**, 7242.
11 L. A. Carpino, M. Beyermann, H. Wenschuh and M. Beinert, *Acc. Chem. Res.*, 1996, **29**, 268.
12 B. F. Bonini, M. Comes-Franchini, M. Fochi, F. Laborio, G. Mazzanti, A. Ricci and G. Varchi, *J. Org. Chem.*, 1999, **64**, 8008.
13 I. Fleming, T. W. Newton and F. Roessler, *J. Chem. Soc., Perkin Trans. 1*, 1981, 2527.
14 A. G. Brook, *Acc. Chem. Res.*, 1974, **7**, 77.
15 (*a*) J. A. Soderquist and C. L. Anderson, *Tetrahedron Lett.*, 1988, **29**, 2425; (*b*) J. A. Soderquist and C. L. Anderson, *Tetrahedron Lett.*, 1988, **29**, 2777.
16 A. Fürstner, G. Kolleger and H. Weidmann, *J. Organomet. Chem.*, 1991, **414**, 295.
17 (*a*) F. N. Tebbe, G. W. Parshall and G. S. Reddy, *J. Am. Chem. Soc.*, 1978, **100**, 3611; (*b*) S. H. Pine, *Org. React.*, 1993, **43**, 1.
18 L. Clawson, S. L. Buchwald and R. H. Grubbs, *Tetrahedron Lett.*, 1984, **25**, 5733.
19 A. N. Petasis and E. I. Bzowej, *J. Am. Chem. Soc.*, 1978, **100**, 3611.
20 A. N. Petasis and S.-P. Lu, *Tetrahedron Lett.*, 1995, **14**, 2393.
21 Due to the unsatisfactory rearrangement of (*S*)-**6a** only the enantiomeric purity of **6b** was determined. Daicel Chiralcel OD–H column, 150 × 4.6 mm, 99.75 : 0.25 hexane–IPA, 0.5 mL min^{-1}, retention times (*R*)-**6b** 7.5 mins, (*S*)-**6b** 8.4 mins. From optical rotation data for the single enantiomers of **5a**, **3a** and **2a** we assumed no racemisation occurred as the route was identical to that for the synthesis of **6b** and this was verified by later analysis of similar series.
22 Daicel Chiralcel OJ-RH column, 150 × 4.6 mm, 55 : 45 MeCN–H_2O, 0.6 mL min^{-1}, retention times for (*E*)-**7b** 29.0 mins and 31.2 mins.
23 A. D. Kaye and G. Pattenden, *Tetrahedron Lett.*, 1986, **27**, 2033.
24 This temperature is from our observations on attempted enantioselective aza-[2,3]-Wittig rearrangements with chiral benzylic anions. See ref. 3.
25 R. E. Gawley, Q. Zhang and S. Campagna, *J. Am. Chem. Soc.*, 1995, **117**, 11817.
26 (*a*) E. K. Verner and T. Cohen, *J. Am. Chem. Soc.*, 1992, **114**, 375; (*b*) R. Hoffmann and R. Brückner, *Angew. Chem., Int. Ed. Engl.*, 1992, **31**, 647; (*c*) K. Tomooka, T. Igarishi, M. Watanabe and T. Nakai, *Tetrahedron Lett.*, 1992, **33**, 5795; (*d*) K. Tomooka, T. Igarishi, N. Komine and T. Nakai, *Synth. Org. Chem. Jpn.*, 1995, **53**, 480.
27 K. Takenouchi, M. Tabe, K. Watanabe, A. Hazato, Y. Kato, M. Shionoya, T. Koike and E. Kimura, *J. Org. Chem.*, 1993, **58**, 6895.
28 G. W. Kabalka, N.-S. Li and R. D. Pace, *Synth. Commun.*, 1995, **25**, 2135.
29 Reactions were attempted with longer reaction times, higher concentrations of Boc_2O, in the presence of DMAP and higher boiling DMF.
30 Daicel Chiralcel OD–R column, 250 × 4.6 mm, 70 : 30 MeCN–H_2O, 0.7 mL min^{-1}, retention times for (*R*)-**9a** 14.2 mins, (*S*)-**9a** 16.0 mins and (*S*)-**9b** 11.6, (*R*)-**9b** 16.2.
31 J. Åhman and P. Somfai, *Synth. Commun.*, 1995, **25**, 2301.
32 R. E. Ireland and R. S. Meissner, *J. Org. Chem.*, 1991, **56**, 4566.
33 Daicel Chiralcel OD–R column, 250 × 4.6 mm, 52.5 : 47.5 MeCN–H_2O, 0.5 mL min^{-1}, retention times (*E*,*S*)-**13b** 59.7 mins and (*E*,*R*)-**13b** 63.6 mins.
34 G. Buchi and H. Wuest, *J. Am. Chem. Soc.*, 1978, **100**, 294.
35 (*a*) G. Dryhurst, *Periodate Oxidation of Diols and other Functional Groups*, Pergamon Press, New York, 1970; (*b*) D. N. Gupta, P. Hodge and J. E. Davies, *J. Chem. Soc., Perkin Trans. 1*, 1981, 2970.
36 J. M. Padron, G. Kokotos, T. Martin, T. Markidid, W. A. Gibbons and V. S. Martin, *Tetrahedron: Asymmetry*, 1998, **9**, 3381.
37 The corresponding TBS protected serieswas synthesised, but this suffered from a difficult selective Boc deprotection step that proceeded in only 39% yield.
38 Daicel Chiralcel OD–R column, 250 × 4.6 mm, 80 : 20 MeCN–H_2O, 0.5 mL min^{-1}, retention times for (*S*)-**16** 18.4, (*R*)-**16** 24.0.
39 Daicel Chiralcel AD column, 150 × 2.1 mm, 99.5 : 0.5 hexane–IPA, 0.2 mL min^{-1}, retention times (*E*,*R*)-**17** 8.4 mins, (*E*,*S*)-**17** 13.3 mins.
40 Daicel Chiralcel OD–H column, 150 × 4.6 mm, 99 : 1 hexane–IPA, 0.5 mL min^{-1}, retention times (*S*)-**18** 9.9 mins, (*R*)-**18** 19.0 mins.
41 This assumption is also supported by the sign of the optical rotations (*E*,*R*)-**19** -3.4 (*c* 2.1, $CHCl_3$), (*E*,*S*)-**17** +7.2 (*c* 1.2, $CHCl_3$), (*E*,*S*)-**13b** +8.5 (*c* 1.3, $CHCl_3$).
42 Daicel Chiralcel OD–H column, 150 × 4.6 mm, 99.25 : 0.75 hexane–IPA, 0.5 mL min^{-1}, retention times (*E*,*R*)-**19** 14.6 mins, (*E*,*S*)-**19** 16.1 mins.
43 J. S. Davies, C. L. Higginbotham, E. J. Treemer, C. Brown and R. C. Treadgold, *J. Chem. Soc., Perkin Trans. 1*, 1992, **10**, 3043.