Synthesis of α,α-disubstituted unnatural amino acid derivatives using the aza-[2,3]-Wittig sigmatropic rearrangement

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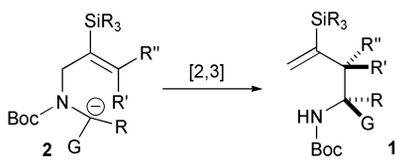
Aza-[2,3]-Wittig rearrangement precursors derived from alanine, valine, phenylalanine and phenylglycine were synthesised with diethylamide and methylester anion stabilising groups. In the amide series only the alanine derived precursor rearranged upon deprotonation with KH. In the ester series the alanine, valine and phenylalanine precursors rearranged successfully with KH. The phenylalanine ester precursor gave an unselective rearrangement whereas rearrangement of the alanine and valine ester precursors gave levels and sense of diastereoselectivity in line with our transition state model. The products are chiral α,α-disubstituted-α-amino acid derivatives possessing two adjacent stereocentres and a vinyl silane synthetic handle.

There is an ever growing interest in the synthesis, pharmacology and conformational properties of non-proteinogenic amino acids. In particular α,α-disubstituted α-amino acids have been the subject of numerous investigations.[1] A large number of these studies have focused on α-aminoisobutyric acid and (−)(*R*)-2-amino-2-methylbutyric acid (2-amino-2-methylbutanoic acid) which are the naturally occurring members of this family. These amino acids are important constituents of a class of microbial peptide antibiotics known as the peptabiols[2] and are thought to play a major role in these peptides' ability to form trans-membrane helical ion channels. Modification of peptides by incorporation of α,α-disubstituted α-amino acids often leads to altered biological activity. These modified peptides can be more stable towards enzymatic degradation,[3] stabilise preferred and often active conformations of peptides,[4] enhance the solubility of hydrophobic peptides in polar solvents,[5] act as enzyme inhibitors[6] and are of special interest as building blocks for peptides. Conformational energy calculations and numerous X-ray studies have highlighted the effect of these unusual amino acids on secondary structures[7] and shown the nature of substituents is of great importance.[8] It is generally accepted that α,α-disubstituted α-amino acids with a methyl group at the C(α) tend to induce 3_{10}- or α-helical conformations when incorporated into peptides.[9] In the acyclic series, two side chains larger than methyl at C(α) tend to induce more extended structures.[10] Although there exists methods for the construction of enantiomerically pure α,α-disubstituted α-amino acids,[11] we believe there is still a need for flexible, complementary methodology which can deliver ever more unusual structures for possible biological applications.

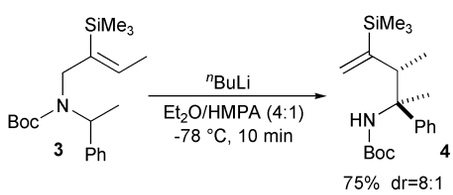
We have developed the acyclic aza-[2,3]-Wittig sigmatropic rearrangement primarily as a synthetic method for synthesising unnatural α-amino acids.[12,13] We have shown that this reaction can deliver good yields of diastereomerically enriched building blocks **1** [R = H, eqn. (1)] for organic synthesis. We have since recognised the potential for the formation of quaternary centres by aza-[2,3]-Wittig rearrangement of precursors **2** [R = alkyl/aryl, eqn. (1)].

In initial studies we found that the substituted benzyl derivative **3** rearranged smoothly to give **4** possessing a quaternary centre [eqn. (2)].[14] We have also shown that the aromatic group in similar products may be selectively oxidised, without epimerisation, to the amino acid,[15] so this result represents a potential route to α,α-disubstituted α-amino acids. In the light



(1)

of our studies which have shown the versatility of the anion stabilising group G (**2**, R = H)[12] and the fact that structurally different α-substituted benzyl amines were limited and not readily available, we have investigated other migrating groups which were closer to the desired amino acid motif. We first investigated rearrangement precursors **2** where the anion stabilising group G was an amide and R = alkyl/aryl.



(2)

Coupling of bromide **5**,[12] readily accessible from phenyldimethylsilylpropyne, with the potassium anion of *N*-Boc-alanine diethyl amide gave the rearrangement precursor **6** in 84% yield [eqn. (3)]. Attempts at the formation of more hindered rearrangement precursors **7**–**9** by the same coupling reaction failed. This was despite trying to enhance the nucleophilicity of the nitrogen anion by employing more polar solvents (DMF, DMSO) or by the addition of 18-crown-6. Increasing the electrophilicity of the allylic halide by including catalytic quantities of n-Bu_4NI or by using the corresponding allylic iodide† and investigating different temperatures also failed to yield the desired products.

We then considered that we could make our desired allylic amines **7**–**9** by a reductive amination procedure between a suitably protected amino acid and the silyl substituted α,β-unsaturated aldehyde **10**.‡§ Under a variety of different reaction conditions we could not induce the amino acid derivatives **11** and α,β-unsaturated aldehyde **10** to couple (eqn. 4).

† From treatment of **5** with NaI in acetone to give a regioisomeric mixture (see Experimental section).

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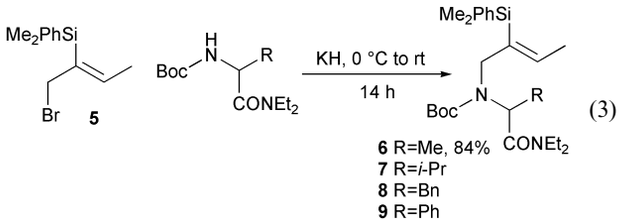
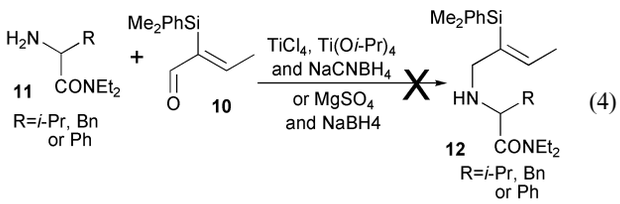


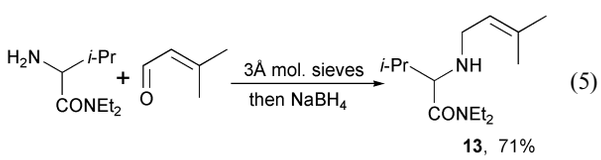
(3)

We speculated that the failure of this reaction was due to the corresponding imine not being formed.



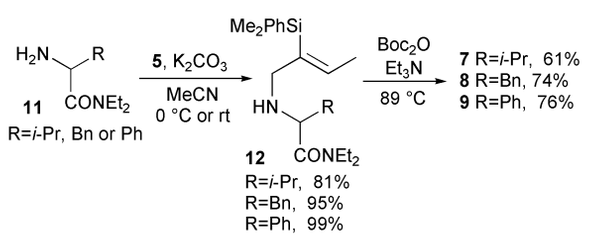
(4)

In subsequent model experiments we found that valine diethyl amide **11** (R = *i*-Pr) and 3-methylbut-2-enal upon treatment with 3 Å molecular sieves and then $NaBH_4$ could give allylic amine **13** in 71% yield [eqn. (5)]. Attempts to form the imine between benzylamine and **10** all failed. It would seem that an α-silyl substituted α,β-unsaturated aldehyde is not a good substrate for imine formation, possibly due to steric hindrance and/or electronic deactivation of the carbonyl group by the silyl substituent.



(5)

The synthesis of substrates **7**–**9** was then approached by the mono-alkylation of **11** with **5** (Scheme 1).[16] This gave good

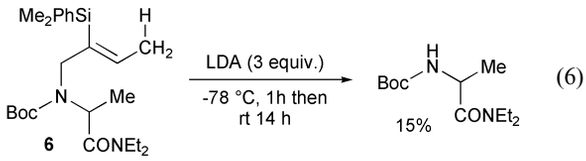


Scheme 1

yields of the valine and phenylalanine derivatives, but the phenylglycine derivative suffered from dialkylation. Consequently **5** was treated with 2 equivalents of **11** (R = Ph) to control mono-alkylation. Protection of the hindered secondary amines with the requisite Boc group was difficult, but was achieved by using Boc_2O in refluxing Et_3N.[17]

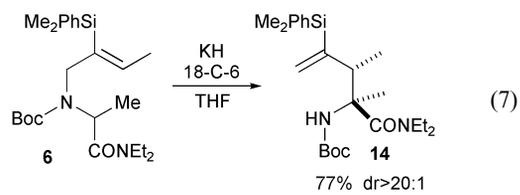
Treatment of **6**–**9** with bases that have proved useful for the aza-[2,3]-Wittig rearrangement,[12] such as lithium amides and alkyllithiums, gave no rearranged products. The main reaction, aside from degradation, gave the elimination product [*e.g.* eqn. (6)].

In earlier studies in which we defined the scope of the aza-[2,3]-Wittig rearrangement we discovered that potassium hydride in combination with 18-crown-6 was a good base for the rearrangement of simpler amide stabilised carbanion



(6)

systems (**2**, R = H, G = $CONMe_2$).[12,13] Treatment of rearrangement precursors **6**–**9** under similar conditions led only to the rearrangement of **6** to give **14** in 77% yield with a diastereomeric ratio (dr) of greater than 20 : 1 by ^{1}H NMR [eqn. (7)]. To determine whether access to the degradation pathway in eqn. (6) was a more favourable pathway to rearrangement, the analogous rearrangement precursors to compounds **6**–**9** that contained a terminal vinyl C-2-silane (*i.e.* **2** R′,R″ = H) were synthesised in an identical fashion. Treatment with a variety of bases led to degradation and recovered starting material. Only the terminal vinyl C-2-silane analogue of **6** gave rearrangement with KH in 76% yield.



(7)

The sense of diastereoselectivity for the rearrangement of **6** was confirmed by single crystal X-ray crystallography of a suitable crystal selected from the bulk sample of **14** which crystallised on standing in the fridge for some weeks.¶ This stereochemical outcome is in accord with our transition state model[18] whereby we assume the sterically larger group ($CONEt_2$) is disposed *anti* to the silyl group (Fig. 1).

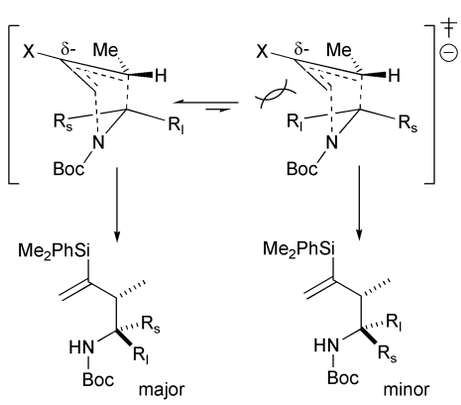


Fig. 1 Transition state model to account for diastereoselection.[18]

Rearrangement precursors **7**–**9** were subjected to the KH–18-C-6 deprotonating conditions and quenched with D_2O after 15 min at 0 °C. We were unable to detect any deuterium incorporation and concluded that these systems could not be deprotonated due to steric inhibition of resonance (Fig. 2). Similar explanations have been forwarded to account for the regioselectivity of deprotonation of β-keto imides containing a bulky chiral auxilliary[19] and the more facile deprotonation of glycine over higher amino acids in the formation of enolates within peptides.[20] We reasoned that the corresponding ester derivatives of **7**–**9** would possess less $A^{1,3}$ strain in the reactive

‡ Prepared from Dess–Martin periodinane oxidation[31] of (*Z*)-2-(phenyldimethylsilyl)but-2-en-1-ol[12] (see Experimental section).

§ The formation of α,β-unsaturated aldimines[32] from the corresponding amine and α,β-unsaturated aldehydes and their subsequent 1,2-reduction[33] with $NaBH_4$ or $NaCNBH_4$ is known.

¶ Crystal data for **14**: $C_{24}H_{40}N_2O_3Si$, M = 432.67, monoclinic, space group: $P2(1)/n$, μ = 0.117 mm^{-1}, R_1 = 0.0447, wR_2 = 0.1001, a = 9.4034(8), b = 18.252(2), c = 15.3571(13) Å, β = 103.981(2)°, U = 2557.7(4) Å^3, temperature of data collection 150(2) K, Z = 5, 953 independent reflections (of 16173 measured), R(int) = 0.074. CCDC reference number 191677. See http://www.rsc.org/suppdata/p1/b2/b207295e/ for crystallographic files in .cif or other electronic format.

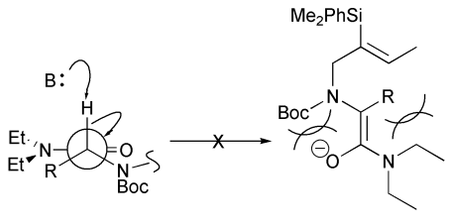
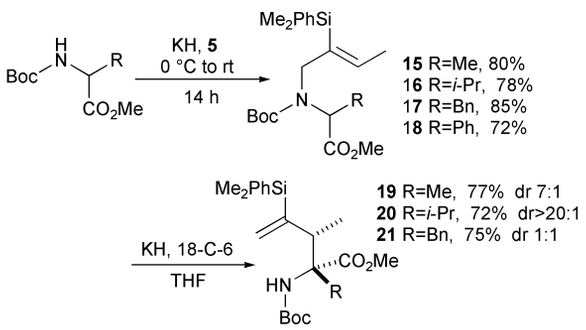


Fig. 2 Steric inhibition of resonance exasperates deprotonation (arbitrary conformation shown).

conformation required for deprotonation. We have already shown that a less hindered glycine derived ester [**2** R,R′ = H, R″ = Me, eqn. (1)] undergo successful rearrangement upon deprotonation with LDA.[12]

All the corresponding ester precursors were prepared from the alkylation of commercially available *N*-Boc methyl ester amino acid derivatives of alanine, valine, phenylalanine and phenylglycine (Scheme 2). The direct alkylation of these



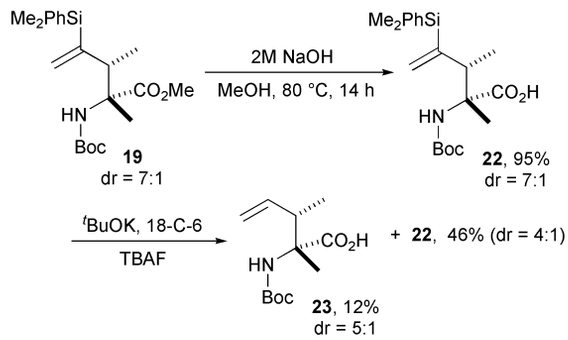
Scheme 2

protected amino acids was successful for the four derivatives investigated. This was in direct contrast to the diethyl amide analogues, for which the alanine derivative could only be alkylated. Presumably hindered rotation about the amide bond forces the bulky amide substituents to exert some detrimental steric effect on the rest of the molecule which inhibits alkylation in some way.

The phenylglycine derivative **18** did not rearrange when treated with KH–18-crown-6 in THF, but did give 100% deuterium incorporation when the reaction was quenched with D_2O. This suggests that the ester stabilised anion is too stable for rearrangement. We have defined a level of reactivity for the anion stabilising groups in aza-[2,3]-Wittig rearrangements whereby if the group exerts a pK_a of less than about 22 on an adjacent C–H bond, then the resultant anion will be too stable to induce rearrangement.[12] The phenyl substituent of the ester enolate from **18** confers extra stability to the enolate anion and effectively impedes the anion towards rearrangement.

Treatment of rearrangement precursors **15**–**17** with KH–18-crown-6 in THF at 0 °C with slow warming to rt for 1 h furnished rearranged products **19**–**21** in good yield, but differing diastereomeric ratios. Based on our transition state model (Fig. 1)[18] and that the alkyl substituents are greater in size than the methyl ester we would expect the diastereoisomer as drawn (**19**–**21**) to be the major compound. The non-selective rearrangement of the phenylalanine derived precursor (**17** to **21**) remains curious to us. The benzyl group is similar in size to a methyl group based on *A* values (7.03 *versus* 7.28 kJ mol^{-1} respectively)[21,22] and we would have expected a similar diastereoselectivity from our transition state model[18] for the rearrangement of **15** and **17**. The isopropyl substituent (*A* value 9.25 kJ mol^{-1})[21] gave the highest diastereoselection, which we expected.

In order to verify the major diastereoisomer of **19** we tried to convert it into the corresponding diethyl amide in an attempt to correlate it with the single crystal X-ray structure determination of **14**. Direct treatment with diethylamine gave only starting material.[23] An alternative strategy involved saponification of **19** with 2 M NaOH in MeOH which gave the amino acid **22** in 95% yield (Scheme 3). This was a difficult reaction to achieve and the

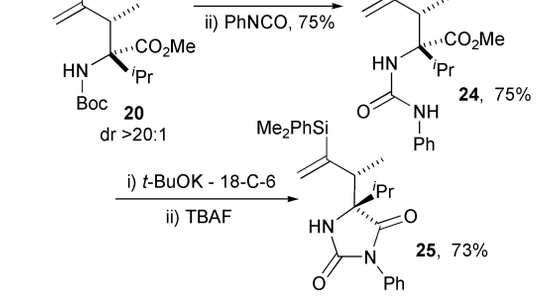


Scheme 3

fact that this reaction took 14 h at 85 °C is testament to the characteristic steric hindrance engendered by α,α-substitution of amino acids. Not surprisingly we were then unable to form a simple amide bond with diethylamine under a variety of standard coupling conditions.

The protodesilylated minor isomer of **22** is in fact known.[24] Protodesilylation under our standard conditons (^{t}BuOK–18-C-6–TBAF)[25] gave a 12% yield of **23** (dr = 5 : 1) along with recovered **22** (dr = 4 : 1, 46% yield). In the crude ^{1}H NMR of **23** the major CHCH_3 resonance appeared at δ 1.04 (d, J = 6.9 Hz) with the minor one at δ 1.09 (d, J = 6.9 Hz). These chemical shifts are comparable with those in the literature[24a] within experimental error [δ 1.03 (minor) and 1.10 (major) respectively] and verifies our assignment as drawn. Although the protodesilylation was not high yielding in this case, from the yields and diastereomeric ratios we can be sure that the major diastereoisomer of **23** is the same as that in **22**. This outcome also fits our stereochemical model whereby we assume that the methyl substituent is larger than the methyl ester and thus prefers to be *anti* to the trialkylsilyl group.

Verification of the structure of the major diastereoisomer of **20** was achieved by manipulating it into a crystalline derivative suitable for single crystal X-ray structure determination. We have prepared other solid derivatives of aza-[2,3]-Wittig products by desilylation and converting the *N*-Boc protected amine to a urea. Removal of the Boc protecting group was followed by treatment with phenyl isocyanate to give urea **24** in 75% yield over 2 steps (Scheme 4). ‖ Although **24** was isolated as



Scheme 4

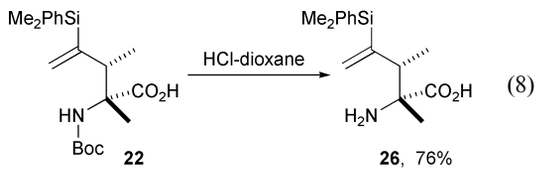
a white chalky solid we were unable to obtain crystals suitable for X-ray determination. Attempted desilylation using our standard conditions[25] resulted in immediate cyclisation to give **25**. Suitable crystals for X-ray structure determination were

‖ Formation of the corresponding *p*-NO_2-phenylurea did not yield crystals suitable for X-ray determination.

prepared which verified structure **25** as the diastereoisomer drawn (Schemes 3 and 4).** The formation of diastereomer **20** was in line with our transition state model (Fig. 1).[18]

In an attempt to render the rearrangements in eqn. (7) and Scheme 2 enantioselective and in line with studies on the alkylation of axially chiral enolates,[26] we synthesised enantiomerically pure samples of **6**, **19** and **20**. Rearrangement under identical conditions led only to racemic products as measured by polarimetry.

To illustrate the synthesis of α,α-disubstituted amino acids, **22** could be Boc deprotected to give amino acid **26** ([eqn. (8)]. This unique structure represents an unusual amino acid in its own right, but in addition possesses the vinylsilane synthetic handle which is readily transferable to a variety of other functionalities.[27]



(8)

We have shown that the aza-[2,3]-Wittig sigmatropic rearrangement can be used for the stereoselective synthesis of chiral α,α-disubstituted α-amino acids. Attempts to use an amide group as the anion stabilising group revealed that the alanine derived precursor **6** defines the steric limit for a successful rearrangement. Only the relatively small base KH was able to effect deprotonation and initiate rearrangement. Other sterically more hindered amino acid amide precursors (**7**–**9**) could not be deprotonated due to steric inhibition of resonance. The corresponding ester derivatives benefit from less $A^{1,3}$ strain in the developing ester enolate anion upon deprotonation. Alanine, valine and phenylalanine derived ester precursors (**15**–**17**) all rearranged in good yields. The phenylglycine derived ester precursor (**18**) formed too stable an anion to undergo [2,3] rearrangement. The alanine and valine ester precursors gave good diastereoselectivities with the magnitude and sense of diastereoselectivity in line with our transition state model. The rearrangement of the phenylalanine ester precursor was strangely unselective. This methodology provides a complimentary synthesis of a unique class of hindered amino acid derivatives possessing 2 vicinal stereocentres and a vinylsilane synthetic handle. These results underpin our own studies in the synthesis of more complex amino acid derivatives which will be reported in due course.

Experimental

General details

Unless otherwise stated all reactions were carried out under an atmosphere of nitrogen. All glassware was flame dried and allowed to cool under a steam of nitrogen before use. THF was distilled under an atmosphere of dry nitrogen from potassium benzophenone ketyl. Diethyl ether was distilled under a dry atmosphere of nitrogen from sodium benzophenone ketyl. All other reagents were purified or dried according to standard literature methods. Water was distilled. *N*-Butyllithium was used as a solution in hexanes, standardised with *N*-pivaloyl-*o*-toluidine. Thin layer chromatography was performed on Polygram® SIL G/UV_{254} 0.25 mm silica gel precoated plastic sheets with fluorescent indicator. Sheets were visualised using ultraviolet light (254 nm) and/or $KMnO_4$ solutions. Flash column chromatography was carried out using Fluorochem silica gel 60, 35–70 μ. ^{1}H NMR and ^{13}C NMR spectra were recorded at 400 and 100.6 MHz respectively as dilute solutions in deuteriochloroform unless otherwise stated. All chemical shifts (δ) are quoted in ppm and coupling constants (J) in Hz. Coupling constants are quoted twice, each being recorded as observed in the spectrum without averaging. ^{13}C multiplicities were assigned using a DEPTsequence. Residual signals from the solvents were used as an internal reference. Mass spectra were acquired on a VG micromass 70E, VG Autospec or Micromass LCTOF. Melting points are uncorrected and were recorded on a Reichert melting Point Apparatus. Elemental analyses were performed by the microanalysis service of the School of Chemistry, University of Nottingham on an Exeter Analytical Inc. CE440 elemental analyzer.

General procedure A—alkylation of *N*-Boc protected amino acid esters/amides

A solution of *N*-Boc protected amino acid ester/amide (1 equiv.) in THF (2 mL mmol^{-1}), was added, *via* cannular, to a stirred suspension of KH (1.2 equiv. of a 35% dispersion in mineral oil, washed twice with hexane) in an equal volume of THF at 0 °C (ice bath). After stirring for 1 h, a solution of electrophile (1.05 equiv.) in THF (total concentration 5 mL mmol^{-1}) was added and the reaction stirred for 1 h at 0 °C followed by 14 h at rt. Saturated aqueous $NaHCO_3$ was added, and the THF removed *in vacuo*. The residue was partitioned between saturated aqueous $NaHCO_3$ and Et_2O, separated and the aqueous layer further extracted with Et_2O. The combined organics were dried ($MgSO_4$) and concentrated *in vacuo* to give crude products, which were purified by flash-column chromatography (eluting with EtOAc–hexane).

General procedure B—standard procedure of aza-[2,3]-Wittig sigmatropic rearrangements using KH as base

A solution of precursor in THF (2 mL mmol^{-1} + 1 mL mmol^{-1} wash) and then solid 18-crown-6 (1.0 equiv.) was added to a stirred suspension of KH (2.5–3.0 equiv. of a 35% dispersion in mineral oil washed twice with hexane) in THF (2 mL mmol^{-1}) at 0 °C. After 10 min at 0 °C the reaction mixture was warmed to rt for a further 2 h before being cooled to 0 °C and quenched with pH 7 phosphate buffer (~2 mL). The mixture was then diluted with Et_2O, the organic layer separated and the aqueous layer further extracted with Et_2O. The combined organics were washed twice with H_2O and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The resulting crude products were purified by flash-column chromatography (eluting with EtOAc–hexane).

General procedure C—formation of *N*,*N*-diethyl-(*N*-Boc) amino acid amide

To a solution of Boc-amino acid in tetrahydrofuran (3 mL mmol^{-1}) at rt was added Et_3N (1 equiv.). The resulting mixture was cooled to −30 °C and treated with ethyl chloroformate (1 equiv.). After stirring for 40 min the now white suspension was treated with Et_2NH (2 equiv.). The resulting mixture was stirred for a further 40 min at this temperature and at 1.2 h at rt. The solvent was removed in *vacuo*; the residue dissolved in CH_2Cl_2 and washed sequentially with 0.1 M HCl; 7% K_2CO_3; H_2O and brine. Drying ($MgSO_4$) and concentration furnished the crude products, which were purified by column chromatography (eluting with EtOAc–hexane).

General procedure D—formation of *N*,*N*-diethyl amino acid amide

To a solution of *N*,*N*-diethyl-(*N*-Boc) amino acid amide, prepared in general procedure C, in CH_2Cl_2 (0.9 mL mmol^{-1}) was

** Crystal data for **25**: $C_{24}H_{31}N_2O_2Si$, M = 406.59, monoclinic, space group: $P2(1)/n$, μ = 0.121 mm^{-1}, R_1 = 0.0500, wR_2 = 0.134, a = 12.9645(10), b = 7.7486(6), c = 23.421(2) Å, β = 92.292(1)°, U = 2350.0(5) Å^3, temperature of data collection 150(2) K, Z = 5.581 independent reflections (of 21085 measured), R(int) = 0.037. CCDC reference number 191678. See http://www.rsc.org/suppdata/p1/b2/b207295e/ for crystallographic files in .cif or other electronic format.

added with CF_3CO_2H (0.9 mL $mmol^{-1}$) at rt. After stirring for 2 h the reaction was washed with 1 MNaOH, dried ($MgSO_4$) and the solvent removed in *vacuo* to yield the crude product, which was >95% pure by ^1H NMR, and was used without further purification.

(1*S**, 2*R**)-*N*-*tert*-Butoxycarbonyl-1,2-dimethyl-1-phenyl-3-trimethylsilylbut-3-enylamine (4)

To a stirred solution of **3**[14] (98.0 mg, 0.28 mmol) was added dropwise *n*-BuLi (156 μL of a 2.5 M solution in hexane, 0.34 mmol, 1.2 equiv.) in a 4 : 1 mixture of Et_2O–HMPA at −78 °C. After stirring for 10 min the reaction was quenched by the addition of MeOH (0.2 mL), warmed to rt and partitioned between saturated aqueous $NaHCO_3$ (5 mL) and Et_2O (5 mL). The mixture was separated and the aqueous phase further extracted with Et_2O (2 × 5 mL). The combined organics were washed H_2O (4 × 5 mL), dried ($MgSO_4$), filtered through a short plug of silica (to remove any remaining HMPA) and concentrated *in vacuo*. Purification by flash-column chromatography (eluting with 10% Et_2O–light petroleum) furnished **4** (73 mg, 75%) as a colourless oil in an inseparable 8 : 1 mixture of diastereoisomers; IR ν_{max} 3456, 2974, 1691, 1248 cm^{-1}; ^1H NMR (250 MHz, d_6-DMSO) δ 0.06 (9H, s), 0.83 (3H, d, J = 7.0), 1.20–1.38 (9H, br m), 1.62 (3H, s), 2.77 (1H, br q, J = 6.7), 5.19 (1H, d, J = 2.1), 5.48 (1H, d, J = 2.1), 6.24 (1H, br s), 7.20–7.30 (5H, m); MS (CI^+) 348 (M^+); HRMS $C_{20}H_{34}NO_2Si$: calcd. 348.2359, found 348.2347.

N,*N*-Diethyl-(*N*-Boc)-alanine amide

N-Boc-alanine (2.60 g, 13.7 mmol) was converted to *N*,*N*-diethyl-(*N*-Boc)-alanine amide according to general procedure C. The resulting crude oil (3.59 g) was purified by flash-column chromatography (15×4 cm, eluting with 20% EtOAc–hexane) and gave the diethyl amide as a pale yellow oil (3.12 g, 93%); IR ν_{max} (thin film) 3322, 2977, 1705, 1641, 1456, 1174 cm^{-1}; ^1H NMR δ 1.09 (3H, t, J = 7.1), 1.20 (3H, t, J = 7.1), 1.27 (3H, d, J = 6.8), 1.41 (9H, s), 3.24 (1H, dq, J = 13.7, 7.1), 3.31 (1H, dq, J = 14.4, 7.1), 3.38 (1H, dq, J = 14.2, 7.1), 3.46 (1H, dq, J = 14.1, 7.1), 4.54 (1H, dq, J = 7.5, 6.8), 5.45 (1H, br d, J = 7.9); ^{13}C NMR δ 12.9, 14.6, 19.8, 28.4, 40.2, 41.7, 46.2, 79.4, 155.1, 172.1; MS (FAB) 245 (MH^+); HRMS $C_{12}H_{24}N_2O_3$: calcd. 245.1864, found 245.1865. Anal Calcd. for $C_{12}H_{24}N_2O_3$: C, 58.99; H, 9.99; N, 11.47. Found C, 58.94; H, 10.00; N, 11.48%.

N,*N*-Diethyl-(*N*-Boc)-valine amide

N-Boc-valine (3.00 g, 13.8 mmol) was converted to *N*,*N*-diethyl-(*N*-Boc)-valine amide according to general procedure C. The resulting crude oil (3.15 g) was purified by flash-column chromatography (15 × 4 cm, eluting with 20% EtOAc–hexane) and gave the diethyl amide as a pale yellow oil (2.97 g, 79%); ^1H NMR δ 0.91 (3H, d, J = 6.8), 0.93 (3H, d, J = 6.8) 1.11 (3H, t, J = 7.1), 1.21 (3H, t, J = 7.1), 1.42 (9H, s), 1.92 (1H, dq, J = 13.5, 6.8), 3.15 (1H, dq, J = 14.2, 7.1), 3.33 (1H, dq, J = 14.8, 7.1), 3.45 (1H, dq, J = 14.3, 7.1), 3.60 (1H, dq, J = 14.0, 7.1), 4.34 (1H, dd, J = 9.4, 6.6), 5.25 (1H, br d, J = 9.4). All other spectroscopic data was in agreement with the literature.[28]

N,*N*-Diethyl-(*N*-Boc)-phenylglycine amide

N-Boc-phenylglycine (3.30 g, 13.1 mmol) was converted to *N*,*N*-diethyl-(*N*-Boc)-phenylglycine amide according to general procedure C. The resulting crude oil (3.83 g) was purified by flash-column chromatography (15 × 4 cm, eluting with 20% EtOAc–hexane) and gave the diethyl amide as a yellow oil (3.78 g, 93%); IR ν_{max} (thin film) 3416, 3316, 2976, 2933, 1711, 1642, 1484, 1456, 1169 cm^{-1}; ^1H NMR δ 0.94 (3H, t, J = 7.1), 1.11 (3H, t, J = 7.1), 1.41 (9H, s), 3.13 (1H, dq, J = 14.7, 7.2), 3.28 (2H, dq, J = 14.5, 7.1), 3.51 (1H, dq, J = 14.0, 7.1), 5.51 (1H, d, J = 7.9), 6.05 (1H, br d, J = 7.8), 7.28–7.39 (5H, m); ^{13}C NMR δ 12.7, 13.7, 28.4, 40.6, 41.6, 55.2, 79.8, 127.8, 128.1, 129.0, 139.1, 155.4, 169.1; MS (FAB) 307 (MH^+); HRMS $C_{17}H_{27}N_2O_3$: calcd. 307.202168, found 307.2024. Anal Calcd. for $C_{17}H_{26}N_2O_3$: C, 66.64; H, 8.55; N, 9.14. Found C, 66.44; H, 8.53; N, 8.93%.

N,*N*-Diethyl-(*N*-Boc)-phenylalanine amide

N-Boc-phenylalanine (3.40 g, 12.8 mmol) was converted to *N*,*N*-diethyl-(*N*-Boc)-phenylalanine amide according to general procedure C. The resulting crude oil (4.11 g) was purified by flash-column chromatography (15 × 4 cm, eluting with 20% EtOAc–hexane) and gave the diethyl amide as a yellow oil (3.98 g, 97%); IR ν_{max} (thin film) 3304, 2977, 1703, 1634, 1455, 1172 cm^{-1}; ^1H NMR δ 0.97 (3H, t, J = 7.1), 1.04 (3H, t, J = 7.1), 1.42 (9H, s), 2.82–3.17 (5H, m), 3.50–3.64 (1H, m), 4.74 (1H, dt, J = 8.5, 6.2), 5.35 (1H, br d, J = 8.6); ^{13}C NMR δ 12.8, 14.2, 40.4, 40.6, 41.7, 51.4, 79.6, 126.8, 128.4, 129.6, 137.1, 155.0, 171.5; MS (FAB+) 320 (M^+); HRMS $C_{18}H_{228}N_2O_3$: calcd. 320.2099, found 320.2101.

(*Z*)-*N*,*N*-Diethyl-*N*-*tert*-butoxycarbonyl-*N*-[2-(phenyldimethylsilyl)but-2-enyl]alanine amide (6)

Alkylation *N*,*N*-diethyl-(*N*-Boc)-alanine amide (3.02 g, 12.4 mmol) with **5** was performed according to general procedure A. The crude mixture (5.21 g) was purified by flash-column chromatography (2 × 15 cm, eluting with 20% EtOAc–hexane) to furnish **6** (4.47 g, 84%) as a pale yellow oil; IR ν_{max} 2973, 2932, 1684, 1650, 1456, 1171 cm^{-1}; ^1H NMR δ 0.40 (6H, s), 1.05 (3H, t, J = 7.1), 1.19 (3H, t, J = 7.1), 1.23 (3H, d, J = 6.9), 1.42 (9H, s), 1.59 (3H, dt, J = 7.1, 2.1), 3.15–3.27 (2H, br m), 3.44–3.51 (1H, br m), 3.60 (1H, dq, J = 14.4, 7.2), 3.83 (1H, dt, J = 18.1, 1.8), 3.99 (1H, br d, J = 18.1), 5.19 (1H, br m), 5.93 (1H, q, J = 6.8), 7.32–7.36 (3H, m), 7.53–7.54 (2H, m); ^{13}C NMR δ −1.6, 12.9, 14.6, 16.1, 17.5, 28.4, 40.4, 41.8, 47.9, 49.5, 79.7, 127.8, 128.9, 133.2, 133.8, 139.1, 155.4, 170.9; MS (ES^+) 433 (MH^+); HRMS $C_{24}H_{41}N_2O_3Si$: calcd. 433.2886, found 433.2898.

(*Z*)-2-(Phenyldimethylsilyl)but-2-enyl iodide

To a stirred solution of allyl bromide **5** (458 mg, 1.79 mmol) in acetone (2 mL) at rt was added NaI (538 mg, 3.59 mmol, 2 equiv.). The resulting mixture was brought to reflux for 2 h. After cooling, the mixture was partitioned between Et_2O and H_2O. The organics were washed sequentially with 1 M $NaHSO_3$, H_2O and brine, dried ($MgSO_4$) and concentrated *in vacuo* to give the crude allyl iodide (507mg, 94%.) as a brown oil which was >95% pure by NMR and was used directly in the next step; ^1H NMR δ 0.51 (6H, s), 1.52 (3H, d, J = 6.8), 1.74 (3H, d, J = 6.7), 4.03–4.04 (2H, m), 5.52–5.58 (1H, m), 5.98–5.99 (1H, m), 7.38–7.41 (3H, m), 7.53–7.57 (2H, m).

(*Z*)-2-(Phenyldimethylsilyl)but-2-enal (10)

To a stirred suspension of Dess–Martin periodinane[17] (2.67 g, 6.29 mol, 1.3 equiv.) in CH_2Cl_2 (10 mL) was added (*Z*)-2-(phenyldimethylsilyl)but-2-en-1-ol[12] (1.00 g, 4.85 mmol) in CH_2Cl_2 (10 mL) at rt. and stirred for 1 h. The resulting mixture was washed sequentially with 1 M NaOH, H_2O and brine, dried over $MgSO_4$ and concentration furnished the crude product **10** (0.99 g, quant.) as a colourless oil that required no further purification and was used immediately in the next step; IR ν_{max} 2959, 1679, 1600, 1249, 1111 cm^{-1}; ^1H NMR δ 0.52 (6H, s), 1.88 (3H, d, J = 6.9), 7.29 (1H, q, J = 6.9). 7.35–7.39 (3H, m), 7.50–7.53 (2H, m), 9.53 (1H, s); ^{13}C NMR δ −0.2, 19.9, 129.1, 130.2, 135.1, 139.5, 144.6, 167.9, 200.9; MS (EI^+) 189 (M^+ − Me).

N,*N*-Diethylvaline amide (11, R = *i*-Pr)

N,*N*-Diethyl-(*N*-Boc)-valine amide (2.50 g, 9.18 mmol) was deprotected according to general procedure D and gave **11**

(R = *i*-Pr) as an oil (1.47 g, 93%); ^{1}H NMR δ 0.94 (3H, d, J = 7.1), 0.96 (3H, d, J = 7.1), 1.11 (3H, t, J = 7.1), 1.19 (3H, t, J = 7.1), 1.88 (1H, dq, J = 12.9, 6.6), 2.35 (2H, br s), 3.13–3.29 (2H, m), 3.34 (1H, d, J = 6.2), 3.37–3.46 (1H, br m), 3.55–3.62 (1H, m). All other spectroscopic data was in agreement with the literature.[19]

N,*N*-Diethylphenylalanine amide (11, R = Bn)[29]

N,*N*-Diethyl-(*N*-Boc)-phenylalanine amide (2.50 g, 7.80 mmol) was deprotected according to general procedure D and gave **11** (R = Bn) as an oil (1.58 g, 92%); IR ν_{max} (thin film) 3362, 2973, 2931, 1634, 1453 cm^{-1}; ^{1}H NMR δ 1.06 (3H, t, J = 7.2), 1.10 (3H, t, J = 7.2), 2.08 (2H, br s), 2.82 (1H, dd, J = 13.2, 7.2), 2.98 (1H, dd, J = 13.5, 7.0), 3.03 (1H, dq, J = 13.5, 7.1), 3.14 (1H, dq, J = 13.5, 7.1), 3.19 (1H, dq, J = 13.5, 7.1), 3.54 (1H, dq, J = 13.5, 7.1), 3.86 (1H, br m), 7.21–7.33 (5H, m); ^{13}C NMR δ 12.8, 14.4, 40.5, 41.3, 42.9, 52.8, 126.7, 128.1, 128.5, 129.4, 137.7, 173.6; MS (ES+) 221 (MH$^+$); HRMS $C_{13}H_{21}N_2O$: calcd. 221.1638, found 221.1638.

N,*N*-Diethylphenylglycine amide (11, R = Ph)

N,*N*-Diethyl-(*N*-Boc)-phenylglycine amide (2.50 g, 8.16 mmol) was deprotected according to general procedure D and gave **11** (R = Ph) as an oil (1.63 g, 97%); ^{1}H NMR δ 0.92 (3H, t, J = 7.1), 1.11 (3H, t, J = 7.1), 2.26 (2H, br s), 3.07 (1H, dq, J = 14.3, 7.1), 3.24 (1H, dq, J = 14.5, 7.2), 3.28 (1H. dq, J = 14.2, 7.1), 3.51 (1H, dq, J = 13.9, 7.1), 4.70 (1H, s), 7.28–7.37 (5H, m). All other spectroscopic data was in agreement with the literature.[30]

N,*N*-Diethyl-[N^{α}-(3-methylbut-2-enyl)]valine amide (13)

To a stirred suspension of 3 Å molecular seives (~1 mL in volume) in a solution of *N*,*N*-diethylvaline amide (55 mg, 0.32 mmol, 1.2 equiv.) in CH_2Cl_2 (1.5 mL) was added 2-methylcrotonaldehyde (22 mg, 0.27 mmol) in CH_2Cl_2 (1.5 mL) and the resulting mixture allowed to stir overnight at rt. After filtration through a silica plug and concentration, the crude imine was re-dissolved in EtOH (1 mL). To this was added $NaBH_4$ (12 mg, 0.32 mmol, 1.2 equiv.) in EtOH (1 mL) at 0 °C and the resulting mixture allowed to stir overnight at rt. The reaction was then quenched with H_2O (1 mL) and the mixture subsequently diluted with CH_2Cl_2. The organic layer was separated, the aqueous layer further further extracted with CH_2Cl_2, the combined organics dried ($MgSO_4$) and concentrated *in vacuo*. The resulting crude oil (70 mg) was purified by flash-column chromatography (15 × 1 cm, eluting with 30% EtOAc–hexane) to furnish **14** (45 mg, 71%) as a pale yellow oil; IR ν_{max} 3683, 3027, 2931, 1731, 1626, 1230 cm^{-1}; ^{1}H NMR δ 0.96 (6H, d, J = 6.8), 1.14 (3H, t, J = 7.2), 1.18 (3H, t, J = 7.2), 1.59 (3H, s), 1.67 (3H, s), 1.72–1.79 (1H, m), 1.83 (1H, br s), 2.94–2.99 (1H, m), 3.11–3.27 (4H, m), 3.43 (1H, dq, J = 14.1, 6.8), 3.60 (1H, dq, J = 14.1, 6.8), 5.20–5.24 (1H, m), ^{13}C NMR δ 13.1, 14.5, 17.9, 18.2, 25.7, 29.7, 31.8, 40.2, 41.3, 46.0, 62.4, 77.2, 123.4, 174.0; MS (ES$^+$) 241 (MH$^+$); HRMS $C_{14}H_{28}N_2O$: calcd. 241.2279, found 241.2302.

(*Z*)-*N*,*N*-Diethyl-{N^{α}-[2-(phenyldimethylsilyl)but-2-enyl]}valine amide (12, R = *i*-Pr)

To a stirred suspension of *N*,*N*-diethylvaline amide (**11** R = *i*-Pr, 300 mg, 1.74 mmol) and K_2CO_3 (50 mg, 0.36 mmol, 0.2 equiv.) in MeCN (3 mL) was added a solution of allyl bromide **5** (563 mg, 2.09 mmol, 1.2 equiv.) in MeCN (3 mL) at 3 °C. Further K_2CO_3 (287 mg, 2.08 mmol, 1.2 equiv.) was added and stirring continued at this temperature for 14 h. The mixture was extracted with CH_2Cl_2, the combined organics washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The resulting crude oil (501 mg) was purified by flash-column chromatography (15 × 3 cm, eluting with 20% EtOAc–hexane) to furnish **12**, R = *i*-Pr (438 mg, 82%) as an orange oil; IR ν_{max} 3229, 3048, 2968, 2964, 1635, 1428, 1245 cm^{-1}; ^{1}H NMR 0.30 (3H, s), 0.39 (3H, s), 0.88 (3H, d, J = 7.1), 0.89 (3H, d, J = 7.1), 1.13 (3H, t, J = 7.1), 1.17 (3H, t, J = 7.1) 1.53 (1H, br s), 1.69 (1H, m), 1.73 (3H, d, J = 6.6), 2.83 (1H, d, J = 11.1), 3.0 (1H, d, J = 6.4), 3.21 (1H, dq, J = 13.0, 7.1), 3.24 (1H, dq, J=13.0, 7.1), 3.39 (1H, dq, J = 13.0, 7.1), 3.40 (1H, d, J = 11.1), 3.57 (1H, dq, J = 13, 7.1), 5.96 (1H, q, J = 6.6), 7.31–7.37 (3H, m), 7.54–7.56 (2H, m); ^{13}C NMR (rotamers) δ −0.2, 0.0, 14.1, 15.4, 19.2, 41.6, 42.5, 56.6, 62.9, 128.7, 128.8, 129.1, 129.8. 135.1, 135.3, 137.9, 140.7, 141.1, 141.2, 172.6; MS (ES$^+$) 395 (MH$^+$); HRMS $C_{21}H_{36}N_2OSi$: calcd. 361.2675, found 361.2675.

(*Z*)-*N*,*N*-Diethyl-{N^{α}-[2-(phenyldimethylsilyl)but-2-enyl]}-phenylalanine amide (12, R = Bn)

N,*N*-Diethylphenylalanine amide (**11**, R = Bn, 300 mg, 1.36 mmol) was alkylated as for **12** (R = *i*-Pr). The resulting crude oil (550 mg) was purified by flash-column chromatography (15 × 2 cm, eluting with 20% EtOAc–hexane) to furnish **12**, R = Bn (528 mg, 95%) as a yellow oil; IR ν_{max} 3461, 2968, 2931, 1635, 1427, 1255, 1109 cm^{-1}; ^{1}H NMR 0.36 (3H, s), 0.39 (3H, s), 0.84 (3H, t, J = 7.1), 0.90 (3H, t, J = 7.1), 1.73 (3H, d, J = 6.7) 1.75 (1H, br s), 2.72 (1H, dd, J = 13.0, 8.1), 2.79 (1H, dd, J = 13.0, 6.1), 2.81 (1H, dq, J = 15.0, 7.1), 2.90 (1H, dq, J = 15.0, 7.1), 3.02 (1H, d, J = 11.8), 3.18 (1H, dq, J = 15.0, 7.1), 3.33 (1H, d, J = 11.8), 3.43 (1H, dd, J = 8.2, 6.2), 3.45 (1H, dq, J = 15.0, 7.1), 5.99 (1H, q, J = 6.7), 7.11–7.14 (2H, m), 7.18–7.25 (3H, m), 7.33–7.37 (3H, m), 7.53–7.56 (2H, m); ^{13}C NMR δ −2.5, −2.3, 12.9, 14.0, 14.1, 14.6, 22.6, 31.6, 40.4, 40.6, 40.9, 46.3, 59.5, 126.3, 127.5, 128.1, 128.5, 129.5, 134.0, 138.3, 138.4, 138.9, 173.6; MS (ES+) 409 (MH$^+$); HRMS $C_{25}H_{37}N_2OSi$: calcd. 409.2675, found 409.2649.

(*Z*)-*N*,*N*-Diethyl-{N^{α}-[2-(phenyldimethylsilyl)but-2-enyl]}-phenylglycine amide (12, R = Ph)

N,*N*-Diethylphenylglycine amide (**11**, R = Ph, 760 mg, 3.71 mmol) was alkylated as for **11** (R = *i*-Pr), but using 2 equiv. of **5**. The resulting crude oil (1.12 g) was purified by flash-column chromatography (15 × 3 cm, eluting with 20% EtOAc–hexane) to furnish **12** (R = Ph, 727 mg, 99%, yield based on **5**) as a yellow oil; IR ν_{max} 3685, 2974, 2935, 1635, 1454, 1110 cm^{-1}; ^{1}H NMR 0.42 (3H, s), 0.43 (3H, s), 0.98 (3H, t, J = 7.1), 1.12 (3H, t, J = 7.1), 1.63 (3H, d, J = 6.9), 2.19 (1H, br s), 3.06 (1H, dq, J = 7.3, 14.6), 3.09 (1H, d, J = 12.3), 3.24–3.39 (3H, m), 3.52 (1H, dq, J = 13.8, 6.9) 4.36 (1H, s), 6.29 (1H, q, J = 6.9), 7.24–7.34 (8H, m), 7.55–7.57 (2H, m); ^{13}C NMR δ −2.2, 13.2, 14.7, 14.9, 18.4, 20.3, 31.9, 40.4, 41.5, 47.4, 63.9, 127.6, 128.6, 134.2, 138.7, 138.9, 139.8, 174.3; MS (ES$^+$) 361 (MH$^+$); HRMS $C_{24}H_{35}N_2OSi$: calcd. 395.2518, found 395.2487.

(*Z*)-*N*,*N*-Diethyl-{N^{α}-*tert*-butoxycarbonyl-N^{α}-[2-(phenyldimethylsilyl)but-2-enyl]}valine amide (7)

To a solution of **12** (R = *i*-Pr), (250 mg, 0.69 mmol) in Et_3N (2 mL) was added Boc anhydride (166 mg, 0.76 mmol, 1.1 equiv.) in Et_3N (2 mL). The reaction was brought to reflux for 4 h after which time the solvent was removed *in vacuo*. The resulting crude mixture (272 mg) was purified by flash-column chromatography (2 × 15cm, eluting with 15% EtOAc–hexane) to give **7** (195 mg, 61%) as a pale yellow oil; IR ν_{max} 2967, 2933, 1671, 1638, 1455, 1366, 1110 cm^{-1}; ^{1}H NMR δ 0.38 (3H, s), 0.39 (3H, d, J = 5.0), 0.86 (3H, d, J = 6.8), 0.87 (3H, d, J = 6.8), 1.00 (3H, t, J = 7.1), 1.23 (3H, t, J = 7.1), 1.42 (9H, s), 1.50 (3H, m), 2.28–2.39 (1H, br m), 2.95–3.12 (2H, m), 3.48–3.59 (1H, br m), 3.76–4.13 (3H, br m), 4.38$_{rot}$, 4.65 (1H, d, J = 10.6), 5.70–5.75 (1H, m), 7.31–7.35 (3H, m), 7.53–7.62 (2H, m); ^{13}C NMR

δ −2.0, −1.7, 12.6, 12.8, 14.8, 17.3, 17.5,17.9, 18.3, 19.6, 19.9, 28.0, 28.2, 28.2, 28.5, 40.3, 40.5, 40.9, 41.4, 46.9, 58.9, 60.5, 79.4, 127.5, 127.6, 128.5, 128.6, 131.5, 131.8, 132.7, 133.7, 133.9, 139.1, 156.3, 168.7; MS (ES^+) 483 (MNa^+); HRMS $C_{26}H_{44}N_2O_3SiNa$: calcd. 483.3018, found 482.9908.

(*Z*)-*N*,*N*-Diethyl-{N^{α}-tert-butoxycarbonyl-N^{α}-[2-(phenyldimethylsilyl)but-2-enyl]}phenylalanine amide (8)

Prepared from **12** (R = Bn, 250 mg, 0.61 mmol) in an analogous fashion to **7**. Purified by flash-column chromatography (2 × 15 cm, eluting with 10% EtOAc–hexane) to afford **8** (230 mg, 74%) as a pale yellow oil; IR ν_{max} 2972, 1683, 1647, 1453, 1252, 1168 cm^{-1}; ^1H NMR δ 0.44 (6H, br s), 0.88–1.12 (6H, br m), 1.36 (9H, br s), 1.55 (3H, br d, J = 6.9), 2.87–2.91 (1H, br m), 3.01 (2H, dq, J = 14.2, 7.1), 3.13–3.18 (1H, br m), 3.40–3.49 (1H, br m), 3.62 (1H, dq, J = 14.4, 7.2), 4.03 (2H, br s), 4.96–5.01 and 5.26–5.32 (1H, br m, due to rotamers), 5.82–5.87 (1H, br m), 7.17–7.25 (5H, br m), 7.34–7.36 (3H, br m), 7.53–7.61 (2H, br m); ^{13}C NMR δ −0.4, −0.3, 14.1, 15.8, 18.8, 29.5, 29.7, 38.3, 41.8, 43.0, 56.1, 81.0, 127.7, 129.1, 129.6, 130.2, 131.1, 133.7, 138, 135.2, 140.4, 155.6, 169.6; MS (ES^+) 509 (MH^+); HRMS $C_{30}H_{45}N_2O_3Si$: calcd. 509.3199, found 509.3220. Anal Calcd. for $C_{30}H_{44}N_2O_3Si$: C, 70.82; H, 8.72; N, 5.51. Found C, 70.81; H, 8.82; N, 5.22%.

(*Z*)-*N*,*N*-Diethyl-{N^{α}-*tert*-butoxycarbonyl-N^{α}-[2-(phenyldimethylsilyl)but-2-enyl]}phenylglycine amide (9)

Prepared from **12** (R = Ph, 300 mg, 0.76 mmol) in an analogous fashion to **7**. Purified by flash-column chromatography (2 × 15 cm, eluting with 15% EtOAc–hexane) to afford **9** (279 mg, 74%) as a pale yellow oil; IR ν_{max} (thin film) 2974, 1685, 1654, 1452, 1167 cm^{-1}; ^1H NMR δ 0.09 (3H, s), 0.19 (3H, s), 1.05 (3H, br t, J = 6.5), 1.13 (3H, br t, J = 6.7), 1.34 (3H, br d, J = 5.3), 1.44 (9H br s), 3.12–3.39 (3H, m), 3.47–3.61 (1H, m), 3.78 (1H, br d, J = 17.7), 4.27 (1H, br d, J = 17.9), 5.82, (1H, br m), 5.97_{rot}, 6.22 (1H, br s), 7.15–7.32 (10H, m); ^{13}C NMR δ −1.7, 12.8, 13.8, 14.18, 17.2, 28.3, 28.4, 40.4, 41.7, 49.8, 59.7, 60.4, 79.5, 127.5, 128.2, 128.5, 130.1, 131.3, 133.6, 135.0, 139.1, 155.8, 169.8; MS (ES+) 495 (MH^+); HRMS $C_{29}H_{43}N_2O_3Si$: calcd. 495.3042, found 495.3074. Anal Calcd. for $C_{29}H_{42}N_2O_3Si$: C, 70.40; H, 8.56; N, 5.66. Found C, 70.02; H, 8.31; N, 5.34%.

(2*S,3*R**)-*N*,*N*-Diethyl-2-(N^{α}–*tert*-butoxycarbonylamino)-2,3-dimethyl-4-dimethylphenylsilylpent-4-enamide (14)**

Rearrangement precursor **6** (200 mg, 0.47 mmol) was subjected to the reaction conditions of general procedure B. The crude reaction mixture (211 mg) was purified by flash-column chromatography (12 × 2 cm, eluting with 20% EtOAc–hexane) to give **14** (154 mg, 77%) as a pale yellow oil in an inseparable >20 : 1 mixture of diastereoisomers which crystallised on standing at rt; IR ν_{max} 3421, 2977, 2952, 1737, 1711, 1454, 1368, 1112 cm^{-1}; ^1H NMR δ 0.44 (3H, s), 0.48 (3H, s), 0.93–0.977 (3H, br m), 0.98 (3H, br d, J = 7.0), 0.99–1.08 (3H, br m), 1.34 (9H, s), 1.44 (3H, s), 2.75 (1H, br q, J = 7.0), 3.06–3.54 (4H, m), 4.47 (1H, br s), 5.91 (1H, s), 6.09 (1H, s), 7.37–7.41 (3H, m), 7.52–7.55 (2H, m); ^{13}C NMR δ −2.4, 12.4, 13.8, 17.6, 19.4, 28.3, 41.0, 41.4, 63.7, 79.2, 128.4, 129.6, 132.7, 134.1, 136.9, 150.7, 153.8, 170.8; MS (ES^+) 433 (MH^+); HRMS $C_{24}H_{41}N_2O_3Si$: calcd. 433.2886, found 433.2886.

(*Z*)-*N*-*tert*-Butoxycarbonyl-N^{α}-[2-(phenyldimethylsilyl)but-2-enyl]glycine methyl ester (15)

Alkylation of *N*-Boc-alanine methyl ester, (0.78 g, 3.84 mmol) with **5** was performed according to general procedure A. The crude reaction mixture (1.60 g) was purified by flash-column chromatography (2 × 15 cm, eluting with 7% EtOAc–hexane) to give **15** (1.34 g, 89%) as a colourless oil; IR ν_{max} 2978, 2933, 2952, 1740, 1691, 1368, 1306, 1151 cm^{-1}; ^1H NMR (d^6-DMSO, 95°C) δ 0.42_{rot}, 0.45 (6H, d, J = 2.5), 1.24_{rot}, 1.34 (3H, d, J = 7.0), 1.40_{rot}, 1.41 (9H, s), 1.79_{rot}, 1.67 (3H, d, J = 7.0), 3.62, 3.64_{rot} (3H, s), 3.91, 4.08_{rot} (1H, d, J = 16.1), 4.05, 4.17_{rot} (1H, d, J = 16.1), 4.10 (1H, q. J = 7.0), 6.19, 6.31_{rot} (1H, q, J = 7.0), 7.37–7.39 (3H, m), 7.52–7.57 (2H, m); ^{13}C NMR δ −2.9, −1.5, 14.9, 15.2, 18.2, 18.9, 28.0, 28.3, 29.8, 44.4, 49.8, 51.8, 53.6, 54.0, 80.3, 127.8, 128.9, 129.0, 133.7, 134.0, 136.2, 138.4, 139.1, 142.0, 154.8, 173.1; MS (ES^+) 392 (MH^+); HRMS $C_{21}H_{34}NO_4Si$: calcd. 392.2257, found 392.2291. Anal Calcd. for $C_{21}H_{33}NO_4Si$: C, 64.41; H, 8.49; N, 3.58. Found C, 64.22; H, 8.69; N, 3.59%.

(*Z*)-*N*-*tert*-Butoxycarbonyl-N^{α}-[2-(phenyldimethylsilyl)but-2-enyl]valine methyl ester (16)

Alkylation of *N*-Boc-valine methyl ester, (250 mg, 1.08 mmol) with **5** was performed according to general procedure A. The crude mixture (450 mg) was purified by flash-column chromatography (2 × 15 cm, eluting with 5% EtOAc–hexane) to furnish **16** (349 mg, 77%) as a colourless oil; IR ν_{max} 2964, 2931, 1737, 1682, 1455, 1367, 1109 cm^{-1}; ^1H NMR δ 0.40 (3H, br s), 0.41 (3H, br m), 0.88 (3H, d, J = 6.8), 0.94 (3H, br d, J = 5.3), 1.42–4.48 (9H, br m), 1.60–1.67 (3H, br m), 2.18–2.28 (1H, br m), 3.49–3.62 (3H, br m), 3.70–4.45 (3H, br m), 5.87–6.23 (1H, br m), 7.34–7.35 (3H, m), 7.53–7.55 (2H, m); ^{13}C NMR δ −2.9, −1.5, 14.9, 15.2, 18.2, 18.9, 28.0, 28.3, 29.8, 44.4, 49.8, 51.8, 53.6, 54.0, 80.3, 127.8, 128.9, 129.0, 133.7, 134.0, 136.2, 138.4, 139.1, 142.0, 154.8, 173.1; MS (FAB) 420 (MH^+); HRMS $C_{23}H_{38}NO_4Si$: calcd. 420.2570, found 420.2560. Anal Calcd. for $C_{23}H_{37}NO_4Si$: C, 65.83; H, 8.89; N, 3.34. Found C, 66.19; H, 8.75; N, 3.04%.

(*Z*)-*N*-*tert*-Butoxycarbonyl-N^{α}-[2-(phenyldimethylsilyl)but-2-enyl]phenylalanine methyl ester (17)

Alkylation of *N*-Boc-phenylalanine methyl ester (505 mg, 1.81 mmol) with **5** was performed according to general procedure A. The crude mixture (936 mg) was purified by flash-column chromatography (2 × 15 cm, eluting with 10% EtOAc–hexane) to give **17** (720 mg, 85%) as a colourless oil; IR ν_{max} (thin film) 3065, 2975, 1744, 1699, 1426, 1165 cm^{-1}; ^1H NMR δ 0.38 (3H, br s), 0.37 (3H, s), 1.47 (9H, br s), 1.59 (3H, br d, J = 6.9), 2.77–3.12 (2H, br m), 3.28 (1H, br m), 3.61–6.66 (3H, br m), 3.97–4.10 (1H, br m), 4.25–4.40 (1H, br s), 5.95–6.07 (1H, br m), 7.17–7.23 (3H, br m), 7.28–7.33 (5H, br m), 7.45–7.48 (2H, br m); ^{13}C NMR δ −1.9, −1.6, 18.1, 28.3, 28.6, 36.5, 51.6, 53.9, 53.9, 59.3, 80.4, 80.5, 126.5, 127.7, 128.4, 128.7, 128.8, 129.4, 129.6, 133.6, 133.9, 138.3, 139.1, 142.7, 155.1, 171.7; MS (EI^+) 395 (MH^+); HRMS $C_{27}H_{37}NO_4SiNa$: calcd. 490.2389, found 490.2354.

(*Z*)-*N*-*tert*-Butoxycarbonyl-N^{α}-[2-(phenyldimethylsilyl)but-2-enyl]phenylglycine methyl ester (18)

Alkylation of *N*-Boc-phenylglycine methyl ester, (500 mg, 1.89 mmol) with **5** was performed according to general procedure A. The crude reaction mixture (962 mg) was purified by flash-column chromatography (2 × 15 cm, eluting with 5% EtOAc–hexane) to give **18** (609 mg, 71%) as a colourless crystalline solid, mp 116–119 °C; IR ν_{max} 2978, 2933, 1737, 1714, 1455, 1367, 1108 cm^{-1}; ^1H NMR 0.31 (3H, br s), 0.38 (3H, br s), 1.10_{rot}, 1.40 (9H, br m), 1.59 (3H, d, J = 7.1), 3.27–3.51 (2H, br m), 3.56 (3H, br s), 5.04_{rot}, 6.01 (1H, br s), 6.16–6.23 (1H, br m), 7.09–7.40 (8H, m), 7.48–7.53 (2H, m); ^{13}C NMR δ −1.5, −0.9, −0.3, 0.0, 15.9, 20.1, 29.0, 35.6, 40.2, 53.2, 53.4, 66.5, 66.7, 79.2, 126.6, 128.1, 128.3, 128.4, 128.9, 129.0, 129.3, 129.4, 132.9, 134.4, 134.8, 134.9, 140.6, 145.1, 145.2, 155.0, 173.9; MS (ES^+) 476 (MNa^+); HRMS $C_{26}H_{35}NO_4SiNa$: calcd. 476.2233, found 476.2203. Anal Calcd. for $C_{26}H_{35}NO_4Si$: C, 68.84; H, 7.78; N, 3.09. Found C, 68.86; H, 7.78; N, 3.07 %.

Methyl (2*S,3*R**)-2-(*N*-*tert*-butoxycarbonylamino)-2,3-dimethyl-4-dimethylphenylsilylpent-4-enoate (19)**

Rearrangement precursor **15** (100 mg, 0.26 mmol) was subjected to the reaction conditions of general procedure B. The crude reaction mixture (114 mg) was purified by flash column chromatography (12 × 1 cm, eluting with 5% EtOAc–hexane) to furnish **19** (77mg, 77%) as a colourless oil, in an inseparable 7 : 1 mixture of diastereoisomers; IR ν_{max} 3441, 2968, 2933, 2876, 1713, 1493, 1368, 1313, 1154 cm^{-1}; ^1H NMR δ 0.43 (3H, s), 0.46 (3H, s), 0.97 (3H, d, J = 7.1) 1.38 (9H, s), 1.43 (3H, s), 2.78 (1H, q, J = 7.1), 3.65 (3H, s), 4.80 (1H, s), 5.73 (1H, s), 5.94 (1H, s), [5.67 (1H, s) and 5.88 (1H, s) minor diastereoisomer], 7.35–7.39 (3H, m), 7.52–7.56 (2H, m); ^{13}C NMR (major diastereoisomer only) δ −2.3, −2.1, 17.3, 28.4, 44.3, 52.2, 62.9, 79.5, 128.1, 129.5, 131.2, 134.2, 137.4, 151.0, 154.7, 174.4; MS (ES^+) 414 (MNa^+); HRMS $C_{21}H_{33}NO_4SiNa$: calcd. 414.2076, found 414.2057. Anal Calcd. for $C_{21}H_{33}NO_4Si$: C, 64.41; H, 8.49; N, 3.58. Found C, 64.11; H, 8.76; N, 3.58%.

Methyl (2*S,3*R**)-4-dimethylphenylsilyl-2-isopropyl-3-methyl-2-(*N*-*tert*-butoxycarbonylamino)pent-4-enoate (20)**

Rearrangement precursor **16** (200 mg, 0.47 mmol) was subjected to the reaction conditions of general procedure B. The crude mixture (211 mg) was purifed by flash-column chromatography (12 × 1 cm, eluting with 5% EtOAc–hexane) to give **19** (154 mg, 77%) as a white powdery solid, in an inseparable >20 : 1 mixture of diastereoisomers, mp 92–95 °C; IR ν_{max} 3422, 3068, 2974, 1731, 1498, 1366, 1251, 1167 cm^{-1}; ^1H NMR δ 0.39 (3H, s), 0.48 (3H, s), 0.71 (6H, br d, J = 6.4), 1.16 (3H, d, J = 7.1), 1.44 (9H, s), 2.01–2.11 (1H, br m), 3.48–3.57 (1H, br m), 3.68 (3H, br s), 4.89 (1H, s), 5.59 (1H, s), 5.86 (1H, s), 7.35–7.36 (3H, m), 7.56–7.58 (2H, m); ^{13}C NMR δ −1.9, −0.9, 17.5, 18.1, 18.7, 28.4, 33.7, 43.8, 51.6, 68.2, 79.2, 127.9, 129.0, 129.5, 134.2, 139.4, 152.4, 154.9, 172.5; MS (FAB) 420 (MH^+); HRMS $C_{23}H_{38}NO_4Si$: calcd. 420.257012, found 420.2583. Anal Calcd. for $C_{23}H_{37}NO_4Si$: C, 65.83; H, 8.89; N, 3.34. Found C, 65.84; H, 8.77; N, 3.13%.

Methyl (2*S,3*RS**)-2-benzyl-2-(*N*-*tert*-butoxycarbonylamino)-4-dimethylphenylsilyl-3-methylpent-4-enoate (21)**

Rearrangement precursor **17** (160 mg, 0.34 mmol) was subjected to the reaction conditions of general procedure. The crude mixture (180 mg) was purified by flash column chromatography (12 × 1 cm, eluting with 7% EtOAc–hexane) to give **21** (126 mg, 79%) as a colourless oil, in an inseparable 1 : 1 mixture of diastereoisomers; IR ν_{max} 3421, 2972, 1712, 1495, 1366, 1165 cm^{-1}; ^1H NMR δ 0.34 and $0.45_{diast.}$ (3H, s), 0.38 and $0.46_{diast.}$ (3H, s), 1.20 and $1.28_{diast.}$ (3H, d, J = 7.2), 1.44 and $1.49_{diast.}$ (9H, s), 3.01 and $3.42_{diast.}$ (1H, d, J = 13.4), 3.30 and $3.50_{diast.}$ (1H, q, J = 7.2), 3.53 and $3.75_{diast.}$ (3H, s), 3.68 and $4.11_{diast.}$ (1H, d, J = 13.4), 5.22 and $5.58_{diast.}$ (1H, br s), 5.59 and $5.63_{diast.}$ (1H, s), 5.78 and $6.03_{diast.}$ (1H, s), 7.06–7.11 (2H, m), 7.14–7.25 (3H, m), 7.31–7.31 (3H, m), 7.43–7.46 (1H, m), 7.55–7.57 (1H, m); ^{13}C NMR δ −2.8, −2.2, −2.0, −1.8, −1.6, 17.7, 17.8, 18.1, 28.6, 38.5, 41.1, 46.1, 52.1, 52.6, 68.1, 68.8, 76.8, 79.2, 126.6, 126.7, 127.7, 128.1, 128.1, 128.9, 130.1, 130.6, 134.0, 136.9, 137.1, 138.3, 138.7, 151.8, 152.5, 154.2, 154.6, 172.8, 172.9; MS (FAB) 468 (MH^+); HRMS $C_{27}H_{38}NO_4SiNa$: calcd. 468.2570, found 468.2563.

(2*S,3*R**)-2-(*N*-*tert*-Butoxycarbonylamino)-2,3-dimethyl-4-dimethylphenylsilylpent-4-enoic acid (22)**

To a stirred solution of **19** (262 mg, 0.67 mmol) in MeOH (6.7 mL) was added 1 M NaOH (6.7 mL). The resulting mixture was brought to 80 °C for 14 h. The reaction was then neutralised with 1 M HCl and the solvent removed *in vacuo*. The residue was partitioned between EtOAc (50 mL) and 1N HCl (50 mL). The aqueous layer was further extracted with EtOAc (2 × 30 mL) and the combined organics washed with H_2O (30 mL), brine (30 mL), dried ($MgSO_4$) then concentrated *in vacuo* to afford the required crude product **22** as a colourless oil (240 mg, 95%); IR ν_{max} ($CDCl_3$) 3421, 3188, 3070, 2957, 2881, 1713, 1413, 1253 cm^{-1}; ^1H NMR δ $0.35_{diast.}$ (3H, s), $0.38_{diast.}$ (3H, s), 0.43 (3H, s), 0.46 (3H, s), 1.03 (3H, d, J = 7.1), $1.04_{diast.}$ (3H, d, J = 7.1), 1.39 (9H, br s), 1.41 (3H, s), $1.44_{diast.}$ (3H, s), 2.88–2.96 (1H, m), 5.84 (1H, br s), $5.6_{diast.}$ (1H, d, J = 1.5), 5.75 (1H, d, J = 1.6), $5.97_{diast.}$ (1H, m), 5.99 (1H, d, J = 1.0), 7.33–7.38 (3H, m), 7.49–7.55 (2H, m); MS (FAB^+) 378.2094 (100%, MH^+, $C_{20}H_{32}NO_4Si$ requires 378.2100), 135 (66%, $PhMe_2Si^+$), 73 (91%, $(CH_3)_3CO^+$), 57 (100%, $(CH_3)_3C^+$).

(2*S,3*R**)-2-(*N*-*tert*-Butoxycarbonylamino)-2,3-dimethylpent-4-enoic acid (23)**

A solution of TBAF (0.8 mL of a 1 M solution in THF, 0.795 mmol) was added to a solution of ^{t}-BuOK (39.3 mg, 0.350 mmol, 2.2 equiv.), 18-C-6 (93 mg, 0.350 mmol, 2.2 equiv.) and H_2O (43 µl of 10% H_2O–THF, 0.238 mmol, 1.5 equiv.) in THF (1 mL) and the reaction mixture was stirred for 48 h. The reaction was then acidified to pH 1 with 1 M HCl and extracted with EtOAc (3 × 15 mL). The combined organic layers were then washed with brine, dried ($MgSO_4$), filtered and evaporated to give an oil which was purified by flash column chromatography (30% EtOAc–hexane) to give **23** (4.3 mg, 12%, dr = 5 : 1) and **22** (26.7 mg, 46%). Data for **23** was in agreement with literature.[24a]

(2*R,3*R**)-4-(Dimethylphenylsilyl)-2-isopropyl-3-methyl-2-(3-phenylureido)pent-4-enoic acid methyl ester (24)**

Anhydrous HCl (0.05 mL of a 4.0 M solution in dioxane, 0.198 mmol, 3.3 equiv.) was added dropwise to **20** (25 mg, 0.06 mmol). The resulting solution was stirred at rt for 2 h. The solvent was removed *in vacuo* and the residue partitioned between Et_2O (10 mL) and satd. aq. $NaHCO_3$ (10 mL). The aqueous layer was further extracted with Et_2O (2 × 5 mL). The combined organics were washed with H_2O (10 mL), brine (10 mL), dried ($MgSO_4$) and concentrated *in va*cuo to afford the amine as a pale yellow oil (19 mg, quantitative). The amine was >95% pure by ^1H NMR and was used directly in the next step; IR ν_{max} (thin film) 3391, 2952, 2878, 1722 cm^{-1}; ^1H NMR δ 0.41 (3H, s), 0.43 (3H, s), 0.73 (3H, d, J = 6.8), 0.81 (3H, d, J = 6.8), 1.02 (3H, d, J = 7.2), 1.41 (2H, br s), 2.17 (1H, sept., J = 6.8), 2.74 (1H, q, J = 7.2), 3.68 (3H, s), 5.60 (1H, d, J = 1.8), 5.73 (1H, m), 7.34–7.37 (3H, m), 7.52–7.55 (2H, m); ^{13}C NMR δ −2.5, 15.2, 17.4, 17.9, 32.6, 42.9, 50.7, 66.9, 127.7, 128.5, 129.2, 134.0, 137.7, 139.2, 153.1; MS (ES^+) 320.2063 (100%, MH^+, $C_{18}H_{30}NO_2Si$ requires 320.2045), 242 (100%, $M^+ - Ph$).

The amine from above (24 mg, 0.075 mmol) in benzene (1.0 mL) was treated with phenyl isocyanate (8.6 µL, 0.078 mmol, 1.05 equiv.). The resulting mixture was stirred at rt for 14 h. The solvent was removed *in vacuo* to afford the crude product (45 mg). Purification by flash column chromatography (1 × 15 cm silica, 20% EtOAc–hexane) gave **24** as a white powder (25 mg, 75%), mp = 158–160 °C; IR ν_{max} (thin film) 3697, 3422, 2927, 2854, 1694, 1601, 1105 cm^{-1}; ^1H NMR δ 0.40 (6H, s), 0.76 (3H, d, J = 6.8), 0.99 (3H, d, J = 6.8), 1.18 (3H, d, J = 7.2), 2.42 (1H, sept. J = 6.8), 3.70 (1H, q, J = 7.2), 3.74 (3H, s), 5.00 (1H, br s), 5.61 (1H, d, J = 1.8), 5.84 (2H, br d, J = 1.2), 7.04–7.08 (1H, m), 7.22–7.37 (7H, m), 7.52–7.55 (2H); ^{13}C NMR δ −2.1, −1.6, 18.2, 18.6, 18.9, 34.1, 40.7, 52.1, 69.2, 120.7, 123.5, 127.9, 129.2, 129.6, 134.2, 139.9, 139.1, 152.6, 153.9, 173.9; MS (ES^+) 439.2386 (100%, MH^+, $C_{25}H_{35}N_2O_3Si$ requires 439.2416), 361 (26%, $M^+ - Ph$)

Cyclic urea 25

To a solution of **24** (70 mg, 0.16 mmol) in THF (1 mL) was added sequentially, H_2O (0.04 mL, 0.24 mmol, 1.5 equiv.),

18-C-6 (58 mg, 0.22 mmol, 1.4 equiv.) and ^{t}-BuOK (25 mg, 0.22 mmol, 1.4 equiv.). The resulting mixture was stirred at rt for 2 h, after which time pH 7 phosphate buffer was added (0.5 mL) and the mixture extracted with EtOAc (3 × 20 mL). The combined organics were dried ($MgSO_4$) and concentrated *in vac*uo to provide a crude intermediate (74 mg). To this crude residue was added TBAF (1.6 mL of a 1.0 M solution in THF, 1.60 mmol, 10.0 equiv.) and the resulting solution stirred over night at rt. The reaction mixture was treated with pH 7 phosphate buffer (0.5 mL) and the mixture partitioned between EtOAc (50 mL) and satd. aq. $NaHCO_3$ (50 mL). The aqueous layer was further extracted with EtOAc (2 × 30 mL). The combined organics were washed with brine (30 mL), dried ($MgSO_4$) and concentrated *in vacuo* to furnish a white solid (80 mg). Purification by column chromotography (1 × 15 cm silica, 10% EtOAc–hexane) furnished, after recrystallisation from Et_2O, **25** as a colourless crystalline solid (65 mg, 73%), mp 120–123 °C; IR ν_{max} (thin film) 3408, 2969, 1775, 1715; ^{1}H NMR δ 0.41 (3H, s), 0.49 (3H, s), 0.71 (3H, d, J = 6.8), 0.80 (3H, d, J = 6.8), 1.27 (3H, d, J = 7.1), 2.31 (1H, sept. J = 6.8), 2.89 (1H, q, J = 7.1), 4.05 (1H, br s), 5.73 (1H, d, J = 1.3), 5.9 (1H, d, J = 0.8), 7.26–7.36 (3H, m), 7.41–7.49 (5H, m), 7.60–7.63 (2H, m); ^{13}C NMR δ −3.9, −2.8, 15.7, 15.8, 16.9, 31.3, 38.9, 69.9, 126.2, 126.4, 128.1, 128.2, 128.6, 129.1, 126.5, 130.1, 131.6, 134.3, 137.1, 151.8, 155.8, 174.5; MS (ES$^+$) 407.2185 (22%, MH^+, $C_{24}H_{31}N_2O_2Si$ requires 407.2154), 329 (100%, M^+ − Ph).

(2*R**,3*R**)-2-Amino-4-(dimethylphenylsilyl)-2,3-dimethylpent-4-enoic acid (26)

Anhydrous HCl (0.15 mL of a 4.0 M solution in dioxane, 0.610 mmol, 5 equiv.) was added dropwise to **22** (46 mg, 0.122 mmol). The resulting solution was stirred at rt for 2 h. The solvent was removed *in vacuo* to furnish the pale yellow product (45 mg). Purification with Dowex 50WX4–100 ion exchange provided amino acid **26** (26 mg, 76%) as a white solid, mp = 134–135 °C; ^{1}H NMR (d^6-DMSO) (major only) δ 0.38 (3H, s), 0.41 (3H, s), 0.98 (3H, d, J = 7.2), 1.25 (3H, s), 2.68 (1H, br q, J = 7.0), 5.53 (1H, d, J = 2.2), 6.17 (1H, d, J = 1.9), 7.37–7.43 (3H, m), 7.52–7.54 (2H, m); ^{13}C NMR (d^6-DMSO) δ −2.5, −2.1, −1.5, −1.3, 13.4, 15.0, 18.0, 18.7, 21.7, 23.6, 30.8, 43.4, 60.7, 63.4, 74.2, 128.5, 128.9, 129.7, 130.3, 131.0, 134.4, 134.8, 139.5, 151.9, 172.7; MS (EI$^+$) 277.1506 (10%, M^+, $C_{15}H_{23}NO_2Si$ requires 277.1498), 135 (81%, $PhMe_2Si^+$), 88 (100%).

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