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Asymmetric aza-[2,3]-Wittig sigmatropic rearrangements: chiral auxiliary control and formal asymmetric synthesis of (2*S*, 3*R*, 4*R*)-4-hydroxy-3-methylproline and (−)-kainic acid†

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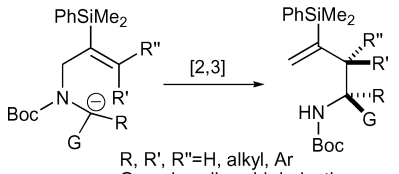
A survey of 16 different chiral auxiliaries and a variety of strategies found that an (−)-8-phenylmenthol ester of a glycine derived migrating group can control the absolute stereochemistry of aza-[2,3]-Wittig sigmatropic rearrangements with diastereoselectivities of *ca.* 3 : 1 with respect to the auxiliary. In two specific examples, *ca.* 50% yields of enantiomerically pure products were obtained after chromatographic purification. These were synthetically manipulated with no erosion of stereochemistry into intermediates that completed formal asymmetric syntheses of (+)-HyMePro and (−)-kainic acid.

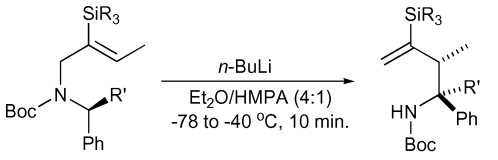
Introduction

We have previously developed the aza-[2,3]-Wittig sigmatropic rearrangement as a synthetic method for the synthesis of unnatural amino acids (eqn. 1).[1] In addition, we have defined the limits of activation and control of diastereoselectivity imparted by the dimethylphenylsilyl group.[2] However, all our studies to date have been racemic, and we wish to report in this paper out first attempts at achieving asymmetric rearrangements, culminating in the use of a chiral auxiliary.



(1)

For the more common oxy-[2,3]-Wittig rearrangement, there exists a number of successful strategies to control the asymmetry of the [2,3]-sigmatropic process. These include: asymmetric transmission from an enantiomerically enriched allylic ether,[3] asymmetric induction from an auxiliary attached to the anionic migrating group[4] or the terminus of the allyl group,[5] an enantioselective ring contraction of a chiral cyclic ether,[6] and the rearrangement of chiral boron ester enolates.[7] In comparison, there are only a few isolated and specific examples of the control of absolute stereochemistry in the aza-[2,3]-Wittig rearrangement. Good enantioselectivities were obtained from the rearrangement of enantiomerically enriched vinylaziridines that were independently reported by the groups of Somfai[8] and Coldham.[9] The use of configurationally defined lithio carbanions derived from enantiomerically enriched tributylstannyl-*N*-*tert*-butoxycarbonyl pyrrolidine gave complicated results, due to epimerisation of the chiral lithio carbanion and also a mixture of competing [1,2] and [2,3] rearrangement pathways.[10] This work, from Gawley *et al.*, verified that the [2,3] rearrangement proceeded with complete inversion of configuration at the lithium-bearing carbanion centre, in accord with precedent in the oxygen series.[11] We were intrigued by the possibilities of a chiral carbanion dictating stereocontrol in our silicon assisted aza-[2,3]-Wittig sigmatropic rearrangements. Analogous attempts to use chiral bases to generate chiral anions in oxy-[2,3]-Wittig systems has only been possible in isolated cases and with only moderate enantioselectivity (<30–60%).[12] The configurational stability of carbanions adjacent to nitrogen atoms can be stabilised by the Boc dipole,[13] enabling even the configurational stability of tertiary benzylic anions at −78 °C.[14] Accordingly, we synthesised the structurally similar and enantiomerically pure aza-[2,3]-Wittig precursors **1a** and **1b** (R′ = Me) and subjected them to anionic rearrangement (eqn. 2). The rearrangements were successful at just under −40 °C to give rearranged products with significant optical rotations.[15] Measurement of the enantioselectivity proved very difficult. Separation of a number of derivatives by chiral HPLC proved impossible, and derivatisation with a number of chiral groups was low yielding and despite giving very favourable results was thought to be ambiguous. However, these experiments led us to tentatively assign the major enantiomer as shown, which is that expected from inversion at the lithium-bearing chiral centre.[16]



(2)

Encouraged by a hint of success from this strategy, we attempted to deprotonate the achiral aza-[2,3]-Wittig precursor **3** (R$_3$ = PhMe$_2$, R′ = H) by using chiral base systems. Examples of very similar α-(*N*-Boc)amino benzylic chiral anions have been generated in the literature with varying degrees of configurational stability.[17] Many attempts using sparteine/BuLi and chiral amide bases[18] were wholly unsuccessful. From our experiments, rearrangement of the less substituted benzylic anion of **3** occurs at temperatures above −40 °C, and we conclude that at this temperature, the rate of epimerisation is faster than the rate of sigmatropic rearrangement. Disappointed that the natural character of this molecular system had defeated our endeavours, we contemplated the more straightforward but synthetically less appealing strategy of using a chiral auxiliary.

† Electronic supplementary information (ESI) available: Synthesis and characterisation of chiral auxiliary rearrangement precursors. See http://dx.doi.org/10.1039/b506198a

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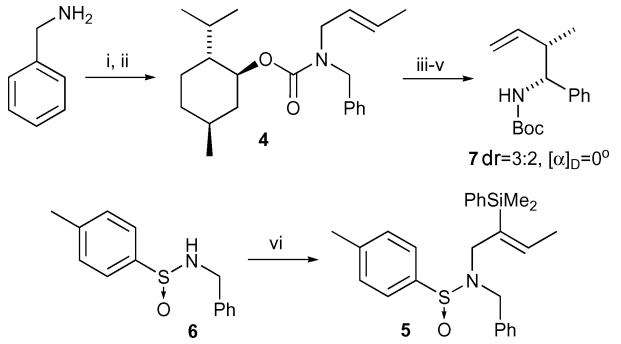
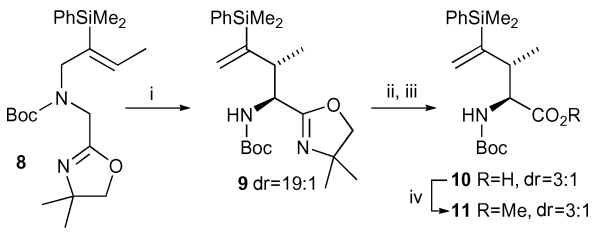
Results and discussion

In parallel with studies investigating a chiral auxiliary attached to the migrating group, we also explored the possibility of a chiral protecting group on nitrogen in our aza-[2,3]-Wittig systems. We inferred, from our studies to determine the scope and limitations of the aza-[2,3]-Wittig sigmatropic rearrangement,[2] that the nature of the nitrogen protecting group had a profound effect on the success of the reaction. We synthesised (+)-*N*-menthyloxycarbonyl-*N*-but-2(*E*)-enylbenzylamine **4** from benzylamine by protection with (+)-menthyl chloroformate followed by crotylation, and synthesised the chiral *N*-sulfinamide **5** by crotylation of the known *N*-benzyl-4-methylbenzenesulfinamide **6** (Scheme 1).[19] Rearrangement of the menthyl precursor **4** gave a 62% yield of the rearranged product, but the complexity of the ^{1}H NMR thwarted any measurement of stereoinduction. Reductive removal of the menthyl carabamate with Red-Al®, followed by Boc reprotection, gave **7**, our very first aza-[2,3]-Wittig rearrangement product.[20] This had an identical diastereoselectivity of 3 : 2 as observed before[20] and exhibited no optical rotation. Rearrangement of **5** did not occur under a variety of standard rearrangement conditions and in that respect was similar to the sulfonamide analogue.[2]



Scheme 1 Reagents and conditions: (i) (+)-menthyl chloroformate, Et_3N, CH_2Cl_2, 91%; (ii) KH, THF, 0 °C; *trans*-$CH_3CH{=}CHCH_2Br$, 0 °C to rt, 91%; (iii) *n*-BuLi, Et_2O–HMPA (4 : 1), −78 to −40 °C, 14 h, 62%; (iv) Red-Al®, PhMe, rt; (v) Boc_2O, CH_2Cl_2, 94% (2 steps); (vi) KH, THF, **13**, 59%.

In the oxy-[2,3]-Wittig sigmatropic rearrangement Nakia had shown that a migrating chiral amide derived from Meyers' oxazoline led to reasonable levels (up to 84%) of diastereoselectivity.[4a,b] Preliminary studies by us using an achiral oxazoline in an aza-[2,3]-Wittig precursor (**8**) revealed that although the rearrangement gave **9** in good conversion (75% with 25% unreacted starting material) and excellent *anti*-stereocontrol, the compound was not configurationally stable (Scheme 2). Attempts at purification of **9** from residual starting material by column chromatography led to degradation and erosion of the *anti*-stereochemistry. Removal of the oxazoline in the presence of the *N*-Boc group necessitated hydrolysis with aqueous base. The oxazoline of **9** was resistant to quaternisation with MeI, the first step of many basic hydrolytic deprotection



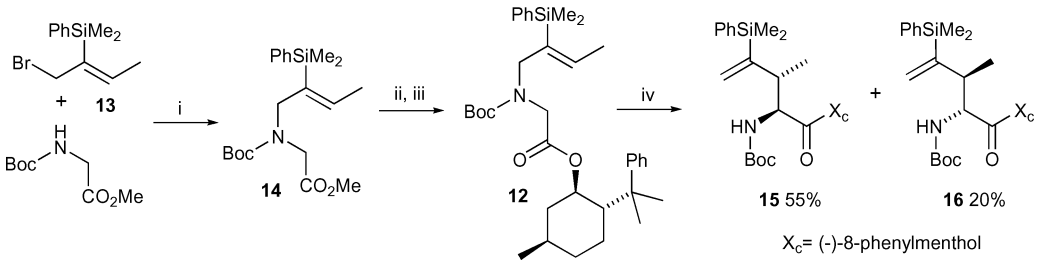
Scheme 2 Reagents and conditions: (i) *n*-BuLi, Et_2O–HMPA (1 : 4), −78 to −40 °C, 14 h, 75% conversion; (ii) *p*-$MePhSO_3Me$, 80 °C; (iii) 15% aq. NaOH, rt, 99% (2 steps); (iv) CH_2N_2, CH_2Cl_2, rt, 83%.

protocols.[21] Quaternisation was eventually achieved by warming **9** in neat methyl *p*-toluenesulfonate, the salt then readily hydrolysed by stirring in aqueous base to give **10** (R=H) in good yield, but with an erosion in *anti*-stereochemistry (Scheme 2).[22] Analysis of the quaternised material revealed epimerisation at the C-1 stereocentre before any hydroxide ion had been added. Due to the configurational instability of **9** imparted by the oxazoline functional group, it was decided to investigate other chiral auxiliaries.

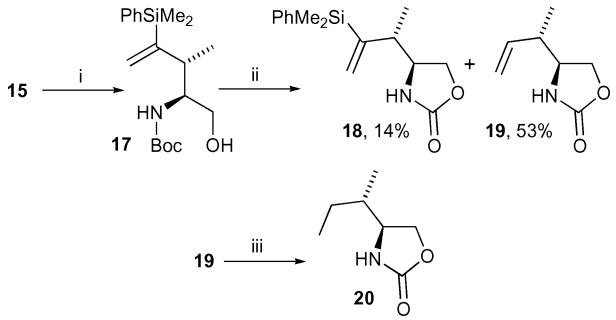
Nakai had gone on to show that (−)-8-phenylmenthyl esters as a migrating group in the oxy-[2,3]-Wittig rearrangement were more effective than chiral oxazolines.[4c] Accordingly we synthesised the aza-[2,3]-Wittig precursor **12**. The most convergent route to **12** was the alkylation of the *N*-anion of *N*-Boc-glycine (−)-8-phenylmenthol ester[23] with **13**, but this gave a complex mixture of products and after laborious separation only gave low yields of **12** under a variety of different conditions. An alternative route involved the *N*-alkylation of *N*-Boc glycine methyl ester with **13**, which gave **14** in 97% yield. Standard saponification gave the corresponding acid (98%), which was esterified with (−)-8-phenylmenthol[24] to give the rearrangement precursor **12** in 93% yield (Scheme 3). This route not only gave access to gram quantities of **12**, but also allowed the screening of other chiral auxiliaries which could be attached as the final step (*vide supra*). Rearrangement of **12** under our general conditions (1.9 equiv. LDA, THF–HMPA, −78 °C to rt)[2] gave a 57% yield of rearranged product with a diastereomeric ratio of 4 : 1.[25] Optimisation of the rearrangement conditions led to the use of KHMDS in THF with DMPU (9%) as co-solvent, at rt for 2 h, and quenching with aq. NH_4Cl. These conditions gave a much higher 87% yield of **15** : **16**, dr = 3 : 1, with only the *anti* distereoisomer detectable by ^{1}H NMR. This optimised rearrangement gave the highest isolated yield of diastereomerically pure **15**. The two isomers had a small separation on silica tlc, but could be efficiently separated by two purifications using Biotage® medium pressure chromatography to give a 55% yield of diastereomerically pure (>95% by ^{1}H NMR) **15** along with the pure minor isomer **16** in 20% yield.

Hydrolysis of the bulky (−)-8-phenylmenthyl auxiliary was not possible,[26] and instead ester **15** was reduced with $LiAlH_4$ to alcohol **17** in a reproducible 79% yield (99% recovery of (−)-8-phenylmenthol), as long as a non-aqueous work up was used (Scheme 4).[27] The ^{1}H NMR of **17**, both as a crude sample and after purification, showed only one diastereoisomer. Rearrangment of achiral **14** at 0 °C instead of the optimal −40 °C gave a 3 : 1 (*anti* : *syn*) mixture of rearranged methyl esters, which were reduced with $LiAlH_4$ as above to give a corresponding 3 : 1 diastereomeric mixture of **17**. The ^{1}H NMR of this sample showed the major diastereoisomer was identical to that obtained from the rearrangement of **12**. The major diastereoisomer from the rearrangement of **14** has been inferred as *anti* by us previously.[2] Therefore rearrangement of (−)-8-phenylmenthyl ester **12** gives only the *anti*-2,3-diastereoisomer, with the observed diastereoisomeric ratio by ^{1}H NMR being equal to the diastereoselectivity exerted by the chiral auxiliary (3 : 1).

To determine the level of asymmetric induction from the rearrangement, protodesilylation of **17** was performed in an attempt to correlate the enantioenriched material to known *N*-Boc-isoleucinol. In the event, treatment with TBAF in refluxing DMSO[28,29] caused incomplete protodesilylation, but cyclisation to the oxazolidinones **18** and **19** (Scheme 4). Desilylated material **19**, upon hydrogenation over platinum, gave the known compound **20** (99%). Unfortunately the reported optical rotation of enantiomerically pure **20** is small [lit.[30] $[a]_D$ + 2.6 (*c* 1.3 $CHCl_3$)], which made our value [$[a]_D$ + 1.6 (*c* 1.3 $CHCl_3$)] ambiguous within error limits. We therefore synthesised authentic samples of racemic- and (+)-**20** according to the literature route,[30] from DL- and L-isoleucine respectively.



Scheme 3 Reagents and conditions: (i) KH, THF, 0 °C to rt, 97%; (ii) NaOH, H_2O–THF, rt, 98%; (iii) DCC, DMAP, (−)-8-phenylmenthol, CH_2Cl_2, −30 °C to rt, 93%; (iv) KHMDS, THF–DMPU (10 : 1), rt, 87%, *dr* = 3 : 1.



Scheme 4 Reagents and conditions: (i) $LiAlH_4$, Et_2O, 0 °C, 79%; (ii) TBAF, THF, DMSO, 135 °C; (iii) H_2, PtO_2, EtOAc, 99%.

Chiral GC analysis confirmed that our synthetic sample of (+)-**20** derived from pure **15** was a single enantiomer, and therefore that the major enantiomer from the rearrangement of **12** was (2*S*, 3*R*)-**15**.[31]

Having optimised the rearrangement using the (−)-8-phenylmenthol auxiliary, we surveyed several other commonly available chiral auxiliaries that covered a wide range of chiral pool families (Fig. 1).[32] Menthol-like auxiliaries **21** and **22** were chosen as they were structurally similar to **12**. Ephedrine-like auxiliaries have received widespread use in controlling the attack of glycine enolates to various electrophiles.[33] Proline-like auxiliaries have been used as stereocontrol elements in a variety of asymmetric reactions.[32] Finally, a small selection of structurally diverse and inexpensive auxiliaries were also screened. The auxiliaries were attached, using DCC, to the acid derived from **14**; the more hindered examples required the use of HOBt, and sometimes elevated temperature.

Rearrangements were performed under the optimised conditions found for **12** [KHMDS, THF–DMPU (10 : 1), rt, 2 h]. Quantification of the rearrangements was carried out tentatively by ^{1}H NMR, with more complicated spectra needing further 2D COSY, HMBC and HMQC experiments. Many of the rearrangement precursors gave broad and multiple signals due to Boc- and amide-rotamers. These characteristics, coupled with the complex mixtures of diastereosiosmers produced from the rearrangments, made interpretation of the ^{1}H NMR spectra very difficult and individual assignments of rearrangement products were not possible. However, an indication of the extent of rearrangement and any diastereoselection could be tentatively estimated from certain ^{1}H NMR signals (Table 1). We planned that any promising auxiliaries would be investigated further, but in the event this was not necessary. The results were recorded on the criteria of isolated yield, *anti*/*syn* diastereoselectivity, and diastereoselectivity with respect to the auxiliary (Table 1). In general, rearrangements were tolerant of most of the auxiliaries, except **23** and **29** which gave recovered starting material despite several attempts. However, in the worst of these (**24**, **25**, **27**, **30** and **33**), it was clear that there was no single major product and we concluded these were not suitable auxiliaries to control the stereochemistry of the rearrangement. The *anti*-selectivity was assumed, as all rearrangements of a secondary stabilised anion performed to date have given the *anti*-(2,3)-diastereoisomer as the major stereoisomer.[2] The menthol-like auxiliaries **21** and **22** gave reduced selectivities compared to (−)-8-phenylmenthol. These results suggest that the additional phenyl substituent of (−)-8-phenylmenthol compared to menthol is important for

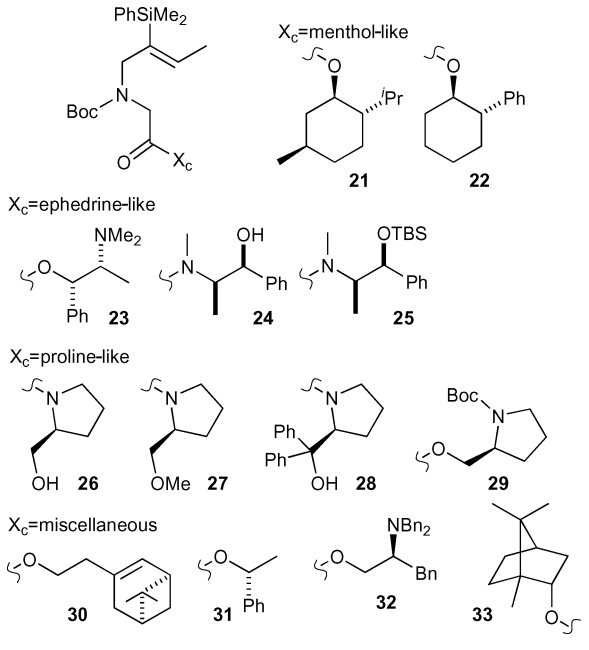


Fig. 1 Different chiral auxiliaries in rearrangement precursor.

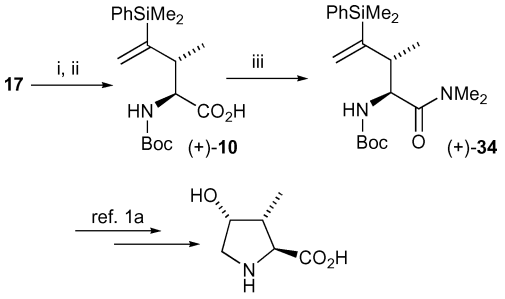
Table 1 Screening of chiral auxiliaries in the aza-[2,3]-Wittig sigmatropic rearrangement

Substrate	Yield/%	*anti*-Selectivity/%	Diastereomeric excess/%
21	57	95[b]	20[b]
22	100[c]	>95	30[d]
23	0	—	—
24	10	>95	—[e]
25	43	—[e]	—[e]
26	58	>95	50[f]
27	69	—[e]	—[e]
28	72	>95	70[g]
29	0	—	—
30	50	—[e]	—[e]
31	100[c]	>95	20[h]
32	56	35[i]	0[i]
33	60	70[j]	—[e]

[a] KHMDS (1.9 equiv.), THF–DMPU (9 : 1), rt, 2 h. [b] From integration in ^{1}H NMR of 4 sets of vinylic signals, δ 5.47–5.65. [c] Conversion. [d] From integration in ^{1}H NMR of vinylic signals, δ 5.71–5.77. [e] Unidentified complex mixture. [f] From integration in ^{1}H NMR of multiplets δ 2.42–2.63. [g] From integration in ^{1}H NMR of triplets δ 4.31–4.43. [h] From integration in ^{1}H NMR of vinylic signals, δ 5.79–5.82. [i] From integration in ^{1}H NMR of 4 sets of vinylic signals, δ 5.18–5.64. [j] From ^{1}H NMR of reduction product **17**.

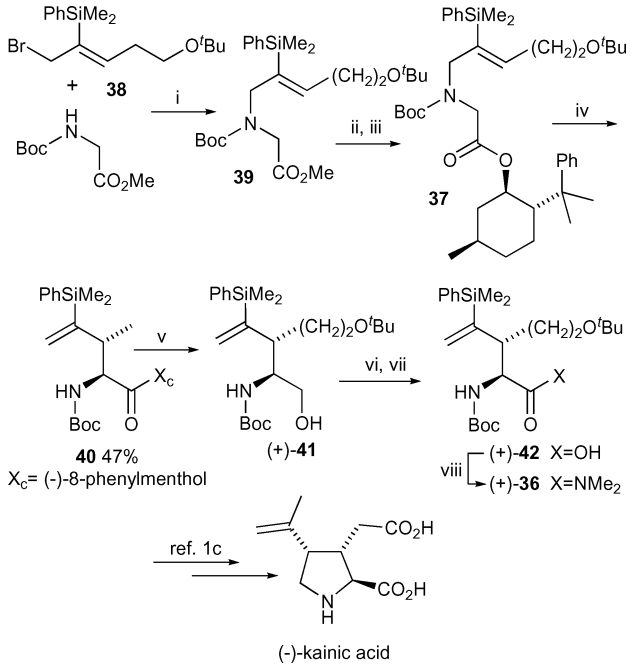
control of stereoselectivity, and alternative aryl groups[34] or napthyl[35] could give better results but at increased cost. The ephedrine-like auxiliaries that underwent rearrangement (**24** and **25**) gave complex ^{1}H NMR spectra that showed no single major product. The miscellaneous auxiliaries investigated (**30**–**33**) gave either complex mixtures, or in the case of **31** only 3 : 2 auxiliary control. The proline derivatives gave two of the most promising results. The standard prolinol auxiliary **26** gave 58% yield of rearranged product with 3 : 1 auxiliary control. This is a lower yield, but identical stereocontrol to the (−)-8-phenylmenthol auxiliary. The diphenylprolinol auxiliary **28** gave a 72% yield of inseparable rearranged diastereoisomers, but with a high 85 : 15 auxiliary control. This result does offer a slight improvement over the (−)-8-phenylmenthol auxiliary in terms of selectivity and the availability of either enantiomer. However, the minor isomer could not be removed from the rearrangement mixture, and the auxiliary is expensive. Despite investigating a wide range of auxiliary structures none offered a significant improvement over the use of (−)-8-phenylmenthol and were not investigated further.

Having found an auxiliary that allowed an efficient material throughput of enantiomerically pure rearrangement products, we investigated the total synthesis of two natural products that we had previously made using the aza-[2,3]-Wittig sigmatropic rearrangement as a key step, but which had been completed in racemic forms. The synthesis of (±)-HyMePro relied upon the formation of rearrangement product **34** (Scheme 5).[1a] We decided to intercept this racemic intermediate with enantiomerically pure material from the rearrangement of **12**. Fortuitously, the major enantiomer **15** contains the correct absolute stereochemistry for the synthesis of naturally occuring (+)-HyMePro. Direct amidation of **15** with a dimethyl amide nucleophile proved unsuccessful due to the necessary basic reaction conditions. Treatment with Weinreb's[36] $Me_2NAl(Me)Cl$ gave clean conversion to a urea derived from attack of the *N*-Boc group (56%). In the event, alcohol **17** was oxidised by a two-step procedure to the carboxylic acid (+)-**10** *via* the crude aldehyde by Dess–Martin periodinane oxidation followed by treatment with buffered sodium chlorite (69% yield over two steps). Amide coupling with an excess of Me_2NH by DCC–HOBt gave enantiomerically pure amide **34** in 78% yield and with no erosion of diastereoselectivity along the four steps from **15** (Scheme 5). The spectral and analytical data of (+)-**34** was identical to the racemic amide that had been prepared earlier[1a] and represents a formal enantioselective total synthesis of (+)-HyMePro.



Scheme 5 Reagents and conditions: (i) Dess–Martin periodinane, CH_2Cl_2, rt; (ii) NaO_2Cl, $(CH_3)_2C{=}CHCH_3$, *t*-BuOH, pH 4 buffer, rt, 69% 2 steps; (iii) Me_2NH (excess), DCC, HOBt, CH_2Cl_2, −30 °C to rt, 78%.

Our synthesis of (±)-kainic acid relied upon the aza-[2,3]-Wittig rearrangement product **36**.[1c] We decided to intercept this intermediate with enantiomerically pure material using the (−)-8-phenylmenthol auxiliary to complete a formal asymmetric synthesis of naturally occurring (−)-kainic acid. Rearrangement precursor **37** was synthesised in an analogous manner to **12** (Scheme 6). The *N*-alkylation of *N*-Boc glycine methyl ester with



Scheme 6 Reagents and conditions: (i) KH, THF, 0 °C to rt, 90%; (ii) NaOH, H_2O–THF, rt, 99%; (iii) DCC, DMAP, (−)-8-phenylmenthol, CH_2Cl_2, −30 °C to rt, 72%; (iv) KH, 18–C-6, THF, 0 °C to rt, 47%; (v) $LiAlH_4$, Et_2O, 0 °C, 70%; (vi) Dess–Martin periodinane, CH_2Cl_2, rt; (vii) NaO_2Cl, $(CH_3)_2C$–$CHCH_3$, *t*-BuOH, pH4 buffer, rt, 75% over 2 steps; (viii) Me_2NH (excess), DCC, HOBt, CH_2Cl_2, −30 °C to rt, 76%.

38[1c] gave methyl ester **39** in 90% yield. Standard saponification gave the corresponding acid (99%), which was esterified with (−)-8-phenylmenthol[37] to give the rearrangement precursor **37** in 72% yield (Scheme 6). Aza-[2,3]-Wittig rearrangement was initiated with KH and 18-C-6 in THF (0 °C to rt, 2 h) to give a 47% yield of diastereomerically pure **40**. The stereochemistry of this major isomer (reaction dr = 3 : 1 with respect to the auxiliary) was assumed to be the same as **15** and as a consequence possessed the absolute stereochemistry required for the synthesis of (−)-kainic acid. Reductive removal of the auxiliary with $LiAlH_4$ (**41**, 70%), two step oxidation to the carboxylic acid (**42**, 75%) and DCC–HOBt coupling with Me_2NH gave (+)-**36** in 76% yield, again with no erosion of diastereoselectivity from **40**. The spectral and analytical data of (+)-**36** was identical to the racemic amide that had been prepared earlier,[1c] and represents a formal enantioselective total synthesis of (−)-kainic acid.

Summary

After surveying a wide range of structurally diverse, privileged chiral auxiliaries, and investigating a range of strategies, we found that an (−)-8-phenylmenthol ester was the most useful at controlling the absolute stereochemistry of the aza-[2,3]-Wittig sigmatropic rearrangement of substrates when attached to a glycine derived migrating group. Although the optimised diastereoselectivity with respect to the (−)-8-phenylmenthol auxiliary was only *ca.* 3 : 1, with complete control of (2,3)-*anti* diastereoselectivity, the material throughput of isolated, pure material was quite high (*ca.*50%). Enantiomerically pure material obtained from two different substrates, after reductive removal of the (−)-8-phenylmenthol auxiliary (**17** and **41**), was used to complete the formal asymmetric synthesis of (+)-HyMePro and (−)-kainic acid. This chiral auxiliary approach is only moderately successful and we are therefore investigating alternative strategies to control asymmetry in aza-[2,3]-Wittig sigmatropic rearrangements.

Experimental

Our general experimental details have been published.[38]

(+)-*N*-Menthyloxycarbonyl-*N*-but-2(*E*)-enylbenzylamine (4)

To a stirred solution of benzylamine (0.20 mL, 1.80 mmol) and Et_3N (0.56 mL, 4.00 mmol, 2.2 eq.) in CH_2Cl_2 (1 mL) was added (+)-menthyl chloroformate (0.43 mL, 2.00 mmol, 1.1 eq.) dropwise at 0 °C. The resulting slurry was stirred for 2 h at rt before being diluted with CH_2Cl_2 (10 mL) and washed sequentially with 1 N HCl (10 mL), H_2O (10 mL) and saturated aq. NaCl (10 mL). The organic phase was dried ($MgSO_4$) and the solvent removed *in vacuo* to give a white solid which was recrystallised from light petroleum to give the protected benzylamine (0.48 g, 91%) as a white fibrous solid mp = 98–99 °C (Found C, 74.6; H, 9.35; N, 4.8. $C_{18}H_{27}NO_2$ requires C, 74.7; H, 9.4; N, 4.8%); $[\alpha]_D$ + 50.0 (*c* 1.1; rt, $CHCl_3$); ν_{max}(film)/cm^{-1} 3408, 2952, 1679, 1522; δ_H (250 MHz; $CDCl_3$) 0.70–2.10 (18H, m, menthyl), 4.35 (2H, d, *J* 5.8, NCH_2Ph), 4.60 (1H, td, *J* 11.0 and 4.6, R_2CHOCO), 4.90 (1H, br.s, N*H*), 7.20–7.40 (5H, m, Ar*H*); δ_C (63 MHz; $CDCl_3$) 16.5, 20.8, 22.1, 23.5, 26.3, 31.4, 34.3, 41.5, 45.0, 47.4, 74.8, 127.2, 127.4, 128.6, 138.8, 156.5; *m*/*z* (EI) 289.2045 (18%, M$^+$. $C_{18}H_{27}NO_2$ requires 289.02042), 150 (100).

A solution of the protected amine (1.36 g, 4.70 mmol) in THF (10 mL) was added dropwise, *via* cannula, to a stirred suspension of KH (1.2 eq. of a 35% dispersion in mineral oil, washed twice with hexane) in THF (10 mL) at 0 °C. After stirring for 1 h a solution of *trans*-CH_3CH=$CHCH_2Br$ (0.58 mL, 5.6 mmol, 1.2 eq.) in THF (5 mL) was added dropwise, *via* cannula, and the reaction stirred for 1 h at 0 °C then 14 h at rt. The reaction was quenched with saturated aq. NH_4Cl and the THF removed *in vacuo*. The residue was partitioned between Et_2O and saturated aq. NH_4Cl, separated and the aqueous phase further extracted with Et_2O (2×). The combined organic layers were dried ($MgSO_4$) and the solvent removed *in vacuo* to give an oil that was purified by flash column chromatography (silica, 5% EtOAc–light petroleum) to give **4** (1.47 g, 91%) as a colourless oil (Found C, 76.9; H, 9.8; N, 4.1. $C_{22}H_{33}NO_2$ requires C, 76.9; H, 9.7; N, 4.1%); $[\alpha]_D$ + 44.4 (*c* 0.9; rt, $CHCl_3$); ν_{max}(film)/cm^{-1} 2955, 1694, 1230; δ_H (250 MHz; $CDCl_3$) 0.70–2.15 (21H, m, menthyl & CH_3CH=), 3.65–3.95 (2H, br.m, NCH_2CH=), 4.43 (2H, br.s, NCH_2Ph), 4.63 (1H, m, R_2CHOCO), 5.30–5.70 (2H, m, C*H*=C*H*), 7.10–7.40 (5H, m, Ar*H*); δ_C (63 MHz; $CDCl_3$) 12.9, 16.3, 17.7, 20.9, 22.1, 23.4, 26.2, 31.4, 34.4, 41.5, 47.4, 49.2, 75.3, 126.3, 127.1, 128.0, 128.4, 138.3, 156.3; *m*/*z* (EI) 343.2508 (16%, M$^+$. $C_{22}H_{33}NO_2$ requires 343.2511), 205 (100), 91 (31).

(1*R, 2*S**)-*N*-Boc-2-methyl-1-phenylbut-3-enylamine (7) and the (1*S**, 2*S**) diastereoisomer (3 : 2)**

Precursor **4** (1.09 g, 3.18 mmol) was treated with *n*-BuLi under standard conditions[39] to give the [2,3]-Wittig rearranged product as an inseparable *ca.* 3 : 2 mixture of diastereoisomers (0.68 g, 62%) as a white amorphous solid mp = 78–79 °C (Found C, 77.2; H, 9.5; N, 4.2. $C_{22}H_{33}NO_2$ requires C, 76.9; H, 9.7; N, 4.1%); $[\alpha]_D$ + 33.0 (*c* 1.0; rt, $CHCl_3$); ν_{max}(film)/cm^{-1} 3336, 2956, 1704, 1496; δ_H (250 MHz; $CDCl_3$) 0.45–1.95 (21H, m, menthyl & CH_3CH=), 2.40 (1H, m, CH_3CHCH=CH_2), 4.20–5.60 (6H, m, N*CH*Ph, R_2CHOCO, CH_3CHCH=CH_2, CH_3CHCH=CH_2 and N*H* by D_2O exchange), 6.95–7.20 (5H, m, Ar*H*); δ_C (63 MHz; $CDCl_3$) (major diastereoisomer) 16.1, 17.1, 20.8, 22.0, 23.5, 26.3, 31.4, 34.3, 41.5, 43.1, 47.4, 58.7, 74.6, 116.0, 126.7, 127.2, 128.1, 139.5, 140.3, 156.0; *m*/*z* (CI) 361 (41, MNH_4^+), 344.2601 (100%, MH$^+$. $C_{22}H_{34}NO_2$ requires 344.2590), 288 (54).

To a stirred solution of the rearranged product (143 mg, 0.42 mmol) in PhH (20 mL) at rt was added dropwise Red-Al® (1.30 mL, 4.16 mmol, 10.0 eq.). After stirring for 14 h the reaction was cooled to 0 °C, quenched by the dropwise addition of saturated aq. NH_4Cl (1 mL) and then extracted with 0.1 N HCl (4 × 10 mL). The combined aqueous phases were adjusted to pH 12–14 by the addition of 6 N NaOH before being extracted with CH_2Cl_2 (4 × 10 mL). The combined organics were dried ($MgSO_4$) and concentrated *in vacuo* to give a crude yellow oil that was immediately dissolved in CH_2Cl_2 (0.5 mL) and treated with Boc_2O (180 mg, 0.84 mmol, 2 eq.). After stirring for 72 h at rt the reaction mixture was adsorbed onto silica gel and purified by flash chromatography (silica, 10% EtOAc–light petroleum) to give **7** (103 mg, 94% over 2 steps). Spectroscopic and analytical data were identical to those reported in the literature.[20]

4-Methylbenzenesulfinic acid benzyl-[2-(dimethylphenylsilanyl)-but-2(*E*)-enyl]amide (5)

A solution of **6** (1.31 g, 5.00 mmol) in THF (10 mL) was added dropwise to a suspension of KH (240 mg, 6.00 mmol, from a 30% dispersion in mineral oil washed twice with hexane) in THF (10 mL) at 0 °C. After stirring for 1 h, 1-bromo-2-(dimethylphenylsilanyl)but-2(*E*)-ene[2] (1.41 g, 5.25 mmol, 1.05 eq.) in THF (2 mL) was added, the reaction then stirred for 1 h at 0 °C and then warmed to rt for 14 h. After addition of saturated aq. $NaHCO_3$ (10 mL) the THF was removed *in vacuo* and the remainder extracted with Et_2O (4 × 20 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to give a brown oil which was purified by flash chromatography (silica, 20% EtOAc–hexanes) to give **5** (1.27 g, 59%) as a white solid mp 72–73 °C; ν_{max}(film)/cm^{-1} 1068; δ_H (400 MHz; $CDCl_3$) 0.33 (3H, s, SiCH_3), 0.37 (3H, s, SiCH_3), 1.62 (3H, d, *J* 6.0, CH_3CH=C), 2.41 (3H, s, Ar–CH_3), 3.67–3.76 (2H, m, NCH_2C=C), 3.88 (1H, d *J* 9.0, NCH_2Ph), 4.04 (1H, d, *J* 9.0, NCH_2Ph), 6.47 (1H, q, *J* 7.0, CH_3CH=C), 7.06–7.53 (14H, m, Ar). δ_C (67.5 MHz; $CDCl_3$) − 0.3(q), 0.0(q), 19.4(q), 22.5(q), 51.9(t), 56.7(t), 140.0(s), 127.4–142.3(Ar), 145.1(d); *m*/*z* (FAB) 434 (MH$^+$).

2-[*N*-Boc-*N*-(2-phenyldimethylsilanylbut-2(*Z*)-enyl)-aminomethyl]-4,4-dimethyl-1,3-oxazoline (8)

Alkylation of 2-*tert*-butoxycarbonylaminomethyl-4,4-dimethyl-1,3-oxazoline[40] (1.44 g, 6.31 mmol) with 1-bromo-2-(dimethylphenylsilanyl)-but-2(*E*)-ene[2] (1 eq.) in an identical manner to the preparation of **5** gave **8** (2.09 g, 79%) as a colourless oil (Found C, 66.0; H, 8.7; N, 6.75. $C_{23}H_{36}N_2O_3Si$ requires C, 66.3; H, 8.7; N, 6.7%); ν_{max}(film)/cm^{-1} 2972, 1704, 1682, 1365, 1249, 732, 702; δ_H (250 MHz; $CDCl_3$) 0.38 (6H, s, $(CH_3)_2$Si), 1.25 (6H, s, =NC$(CH_3)_2CH_2O$-), 1.43 (9H, s, $(CH_3)_3$C), 1.65 (3H, d, *J* 7.0, CH_3CH=), 3.70–4.10 (6H, m, =NC$(CH_3)_2CH_2O$-, NCH_2C=N, NCH_2C=), 6.18 (1H, br.m, CH_3CH=), 7.25–7.55 (5H, m, Ar*H*); δ_C (63 MHz; $CDCl_3$) − 1.6, 17.8, 28.3, 42.1, 53.6, 67.2, 79.2, 79.9, 127.8, 128.8, 133.6, 134.2, 139.0, 141.3, 155.4, 162.5; *m*/*z* (EI) 416.2482 (51%, M$^+$. $C_{23}H_{36}N_2O_3Si$ requires 416.2495), 360 (36), 316 (24), 304 (14), 135 (62), 57 (57).

2-[(1*S, 2*R**)-1-*N*-Boc-amino-2-methyl-3-phenyldimethylsilanylbut-3-enyl]-4,4-dimethyl-1,2-oxazoline (9)**

Precursor **8** (2.03 g, 4.84 mmol) was treated with *n*-BuLi under standard conditions[28] to give a 1 : 3 mixture of recovered **8** and the [2,3]-Wittig rearranged product **9** (dr = 19 : 1, *anti* : *syn*) (2.03 g, 100% crude) that was not purified further; spectroscopic and analytical data were identical to those reported earlier.[2]

(2*S, 3*R**)-2-*N*-Boc-amino-3-methyl-4-phenyldimethylsilanylpent-4-enoic acid (10)**

A stirred mixture of crude 1 : 3 mixture of recovered **8** and aza-[2,3]-Wittig product **9** (*dr* = 19 : 1, *anti* : *syn*) (585 mg, 1.40 mmol) and methyl *p*-toluenesulfonate (261 mg, 1.40 mmol, 1 eq.) was heated at 80 °C (oil bath temperature) for 2 h, after which time stirring became difficult. The reaction was cooled, treated with 15% aq. NaOH (2.5 mL) and stirred for 14 h. The resulting yellow homogeneous solution was acidified to pH 1–3 and extracted with EtOAc. The combined organics were dried ($MgSO_4$) and concentrated *in vacuo* to give a crude mixture of carboxylic acids as a yellow oil (525 mg, >100% mass balance). The material was esterified as below to aid analytical analysis.

Methyl (2*S, 3*R**)-2-*N*-Boc-amino-3-methyl-4-phenyldimethylsilanylpent-4-enoate (11)**

Diazomethane, prepared from the reaction of Diazald® (218 mg, 1.02 mmol, 2 eq.) with 20% aq. KOH (0.4 mL) in EtOH (5 mL), was carried by a stream of N_2 and bubbled through a stirred solution of the crude mixture from above (185 mg, 0.51 mmol) in CH_2Cl_2 (5 mL) at rt. Stirring was continued with N_2 bubbling, until 30 min after the yellow colour had faded. Removal of the solvent *in vacuo* gave a crude yellow oil (180 mg) which was purified by flash column chromatography (silica, 10% EtOAc–light petroleum) to give (2*S**, 3*R**)-**11**, (2*R**, 3*R**)-**11** and the methyl ester of the parent acid of **9** as an inseparable 3 : 1 : 1 ratio (159 mg, 83%). Spectroscopic and analytical data for (2*S**, 3*R**)-**11** was identical to that already reported;[2] (2*R**, 3*R**)-**11**: δ_H (250 MHz; $CDCl_3$) 0.42 (6H, s, $(CH_3)_2Si$), 0.95 (3H, d, *J* 7.0, CH_3CHC=), 1.34–1.45 (9H, m, $(CH_3)_3C$), 2.77 (1H, quin., *J* 6.7, CH_3CHC=), 3.64 (3H, s, CO_2CH_3), 4.36 (1H, dd, *J* 9.5, 5.8, $NCHCO_2CH_3$), 4.86 (1H, d, *J* 8.2, N*H*), 5.50 (1H, m, $CH_3CHC{=}CH_2$), 5.78 (1H, m, $CH_3CHC{=}CH_2$), 7.30–7.55 (5H, m, Ar*H*); ^{13}C NMR not decipherable; *m*/*z* (EI) 377.2007 (10%, M^+. $C_{20}H_{31}NO_4Si$ requires 377.2007), 321 (19), 300 (24), 277 (11), 189 (12), 135 (99), 57 (100). Spectroscopic and analytical data for the methyl ester of the parent acid of **9** was identical to those already reported.[2]

***N*-Boc-glycine (−)-8-phenylmenthol ester**

A solution of Boc-glycine (180 mg, 1.03 mmol), DCC (255 mg, 1.24 mmol) and DMAP (6 mg, 50 μmol) in CH_2Cl_2 (10 mL) was stirred at −30 °C for 10 min. (−)-8-phenyl menthol (1.19 g, 5.13 mmol) in CH_2Cl_2 (6 mL) was then added, and the mixture was slowly warmed to rt. The reaction was then refluxed for 20 h. The solvent was removed *in vacuo* and Et_2O (25 mL) was added. The reaction mixture was filtered through Celite, washed sequentially with saturated aq. $NaHCO_3$ (10 mL), H_2O (10 mL) and brine (10 mL) before being dried ($MgSO_4$) and the solvent removed *in vacuo*. The excess auxiliary was recovered *via* Kugelröhr distillation (bp 132 °C @ 1 mmHg) to leave the product as a colourless oil (402 mg, 96%, lit.[23] yield 93%). δ_H (400 MHz; $CDCl_3$) 0.90 (3H, d, *J* 6.5, CH_3CH), 1.20 (3H, s, CMe_2Ph), 1.27 (3H, s, CMe_2Ph), 1.45 (9H, s, *Boc*), 0.94–2.19 (8H, m, *c-hexyl*), 3.07 (1H, dd, *J* 18.3, 5.9, C*H*NH), 3.29 (1H, dd, *J* 18.0, 5.2, C*H*NH), 4.38 (1H, br. m, N*H*), 4.89 (1H, td, *J* 10.8, 4.5, C*H*OR), 7.12–7.34 (5H, m, *Ar*). All other spectral data were in agreement with literature.[23]

***N*-Boc-*N*-[2-(dimethylphenylsilanyl)but-2(*Z*)-enyl]glycine methyl ester (14)[2]**

***N*-Boc-*N*-[2-(dimethylphenylsilanyl)but-2(*Z*)-enyl]glycine.** A solution of NaOH (60 mg, 1.7 mmol, 3.0 eq.) in water (2 mL) was added to a solution of **14** (212 mg, 0.563 mmol) in THF (2 mL) at rt and was stirred for 21 h. The reaction was acidified with citric acid to pH 3, diluted with Et_2O (10 mL) and separated. The aqueous was re-extracted with Et_2O (10 mL) and the combined organics dried ($MgSO_4$) before the solvents were removed *in vacuo* to afford the title acid as a colourless oil (198 mg, 0.546 mmol, 97%) which was judged >95% pure by ^{1}H NMR. Spectroscopic and analytical data were identical to those already reported.[2]

***N*-Boc-*N*-[2-(dimethylphenylsilanyl)but-2(*Z*)-enyl]glycine-(1*R*, 2*R*, 5*R*)-8-phenylmenthol ester (12)**

A solution of the above acid (10.0 g, 27.6 mmol) in CH_2Cl_2 (135 mL) was cooled to −30 °C, and DCC (5.69 g, 27.6 mmol, 1.00 eq.) and DMAP (330 mg, 2.76 mmol, 0.10 eq.) were added. A solution of (−)-8-phenyl menthol[24] (6.41 g, 27.6 mmol, 1.00 eq.) in CH_2Cl_2 (5 mL) was then added and the resultant yellow solution allowed to warm to rt over 14 h. The solvent was then removed *in vacuo* and replaced with EtOAc (100 mL). The resulting suspension was filtered (Celite®) and the solvent removed *in vacuo* to furnish the crude product as a cloudy oil. Purification by flash column chromatography (5% EtOAc–petroleum ether) gave **12** (14.9 g, 25.7 mmol, 93%) as a thick colourless oil (Found C, 72.75; H, 9.05; N, 2.34. $C_{35}H_{51}NO_4Si$ requires C, 72.75; H, 8.90; N, 2.42); $[\alpha]_D$ + 14.7 (*c* 2.0 in EtOH);. ν_{max}(film)/cm^{-1} 3074, 2824, 1746, 1694; δ_H (400 MHz; $CDCl_3$) 0.50 (6H, s, $SiMe_2$), 0.92–2.21 (29H, m, $CH_2CH(C)OR$ + $CH(CH_3)CH_2CH_2$ + $CH(CH_3)CH_2CH_2$ + CH_3CH + $Me_2C(C)Ph$ + CH_3CH + $CHCMe_2Ph$ + $C{=}CHCH_3$ + *Boc*), 3.26–4.19 (4H, m, CH_2NCH_2), 4.90–4.94 (1H, m, CO_2CH), 6.17–6.24 (1H, m, $C{=}CHCH_3$), 7.19–7.64 (5H, m, CH_{Ar}); δ_C (100 MHz; $CDCl_3$) − 1.6, −1.5, 17.8, 17.9, 21.8, 22.0, 26.3, 26.5, 26.7, 26.8, 27.1, 28.3, 31.3, 31.5, 31.9, 34.5, 34.9, 39.8, 41.8, 41.9, 46.7, 47.0, 50.4, 50.5, 54.2, 75.1, 79.9, 125.1, 125.4, 125.5, 125.8, 127.9, 127.9, 128.4, 128.8, 129.0, 133.2, 133.6, 133.7, 138.7, 139.0, 140.0, 140.6, 140.9, 151.3, 155.2, 155.7, 169.3; *m*/*z* (ES^+) 578.3644 (4%, MH^+ $C_{35}H_{52}NO_4Si$ requires 578.3666) 478 (MH^+-Boc, 38%), 135 (51, $PhMe_2Si^+$), 105 (100, $PhSi^+$), 119 (60, $PhSiMe^+$), 57 (37, $^tBu^+$).

[2*S*,3*R*]-2-*N*-Boc-amino-4-(dimethylphenylsilanyl)-3-methylpent-4-enoic acid [1*R*,2*S*,5*R*]-8-phenylmenthol ester (15) and [2*R*,3*S*]-2-*N*-Boc-amino-4-(dimethylphenylsilanyl)-3-methylpent-4-enoic acid [1*R*,2*S*,5*R*]-8-phenylmenthol ester (16)

A solution of rearrangement precursor **12** (665 mg, 1.15 mmol) in THF (5.8 mL) and DMPU (0.58 mL) at rt was treated with KHMDS (4.37 mL of a 2 M solution in PhMe, 2.19 mmol, 1.90 eq.), and the resultant yellow solution was stirred at rt for 2 h. The reaction was quenched with saturated aq. NH_4Cl (5 mL) and diluted with Et_2O (10 mL). The mixture was separated, and the aqueous phase re-extracted with Et_2O (5 mL). The combined organics were dried ($MgSO_4$) and the solvent removed *in vacuo* to give the crude product as a colourless oil. Purification twice by flash column chromatography (Biotage®, 5% EtOAc–petroleum ether) gave **15** (366 mg, 55%). as a colourless oil followed by the minor diastereoisomer **16** (133 mg, 20%) as a colourless oil. **15**: $[\alpha]_D$ + 6.7 (*c* 2.0 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3444, 3052, 2962, 2927, 1719; δ_H (400 MHz; $CDCl_3$) 0.42 (6H, s, $SiMe_2$), 0.73–1.97 (20H, m, $CH_2CH(C)OR$ + $CH(CH_3)CH_2CH_2$ + $CH(CH_3)CH_2CH_2$ + CH_3CH + $Me_2C(C)Ph$ + CH_3CH + $CHCMe_2Ph$ + $CHCH_3$), 1.44 (9H, s, *Boc*), 2.42 (1H, m, $C{=}CCHCH_3$), 3.94 (1H, t, *J* 8.8, $NHCH$), 4.53 (1H, br d, *J* 8.7, N*H*), 4.76 (1H, td, *J* 10.7, 4.3, CO_2CH), 5.50 (1H, s, $C{=}CH_2$), 5.74 (1H, s, $C{=}CH_2$), 7.15–7.53 (10H, m, CH_{Ar}). δ_C (100 MHz; $CDCl_3$) −2.3, −2.2, 18.5, 21.8, 26.1, 27.0, 27.7, 28.4, 31.4, 34.6, 40.1, 41.7, 41.9, 50.7, 57.7, 76.2, 79.3, 120.8, 125.4, 125.7, 127.9, 128.1, 129.2, 134.1, 138.0, 150.9, 171.9; *m*/*z* (ES^+) 601 (MNa^+, 5%), 578.3664 (MH^+ $C_{35}H_{52}NO_4Si$ requires 578.3666) 478 (MH^+-Boc, 4%), 135 ($PhMe_2Si^+$, 100%), 105 ($PhSi^+$, 42%). **16**: $[\alpha]_D$ + 3.1 (*c* 1.6 in CH_2Cl_2); ν_{max}(film)/cm^{-1} 2955, 2916, 2866, 1720. δ_H (400 MHz; $CDCl_3$) 0.43 (6H, s, $SiMe_2$), 0.74–2.01 (20H, m, $CH_2CH(C)OR$ + $CH(CH_3)CH_2CH_2$ + $CH(CH_3)CH_2CH_2$ + CH_3CH + $Me_2C(C)Ph$ + CH_3CH + $CHCMe_2Ph$ + $CHCH_3$), 1.43 (9H, s, *Boc*), 2.45 (1H, m, $C{=}CCHCH_3$), 4.07 (1H, t, *J* 9.0, $NHCH$), 4.32 (1H, br.d, *J* 8.8, N*H*), 4.78 (1H, td, *J* 10.6, 4.2, CO_2CH), 5.55 (1H, d, *J* 1.9, $C{=}CH_2$), 5.80 (1H, s, $C{=}CH_2$), 7.13–7.56 (10H, m, CH_{Ar}). δ_C (100 MHz; $CDCl_3$); −2.4, −1.4, 18.0, 18.9, 21.8, 22.1, 24.2, 24.3, 26.5, 27.4, 28.4, 28.8, 29.3, 29.8, 31.4, 31.6, 34.5, 34.9, 39.8, 40.3, 41.3, 41.9, 45.4, 50.3, 54.2, 58.6, 73.0, 76.3, 79.5, 125.1, 125.4, 125.7, 125.8, 128.0, 128.1, 128.3, 128.5, 129.0, 129.3, 133.7, 134.1, 137.9, 150.8, 151.1, 151.4, 154.7, 170.6. MS (ES^+): *m*/*z* 600 (28%, MNa^+), 578.3694 (100%, MH^+ $C_{35}H_{52}NO_4Si$ requires 578.3666), 478 (18%, MH^+-Boc).

[1*S*,2*R*]-[3-(Dimethylphenylsilanyl)-1-hydroxymethyl-2-methylbut-3-enyl]carbamic acid *tert*-butyl ester (17)

A suspension of $LiAlH_4$ (90 mg, 2.4 mmol, 3.0 eq.) in Et_2O (3.5 mL) was refluxed for 30 min and cooled to 0 °C. A solution of rearrangement product **15** (460 mg, 0.79 mmol) in

Et_2O (0.5 mL) was then added *via* cannula, and the resultant suspension stirred at 0 °C for 90 min. The reaction was quenched sequentially with H_2O (90 μL), 15% aq. NaOH (90 μL) and H_2O (270 μL). The resulting suspension was diluted with Et_2O (15 mL) and dried ($MgSO_4$) before removal of the solvent *in vacuo*. Purification of the crude product by flash column chromatography (30% EtOAc–petroleum ether) gave **17** (195 mg, 79%) as a colourless oil; $[\alpha]_D$ + 15.3 (*c* 2.0 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3624, 3435, 2956, 2879, 1692; δ_H (400 MHz; $CDCl_3$) 0.44 (3H, s, Si*M*e$_2$), 0.46 (3H, s, Si*M*e$_2$), 1.02 (3H, d, *J* 6.9, C*H*$_3$CH), 1.42 (9H, s, *Boc*), 2.51 (1H, quin., *J* 7.0, C*H*CH$_3$), 2.64 (1H, br s, O*H*), 3.46–3.58 (2H, m, C*H*$_2$OH), 3.69–3.72 (1H, m, NHC*H*), 4.36 (1H, d, *J* 5.5, N*H*), 5.60 (1H, d, *J* 2.3, C=C*H*$_2$), 5.84 (1H, d, *J* 2.2, C=C*H*$_2$), 7.38–7.40 (3H, m, C*H*$_{Ar}$), 7.54–7.57 (2H, m, C*H*$_{Ar}$); δ_C (100 MHz; $CDCl_3$); −2.7, −2.3, 18.8, 28.6, 40.1, 56.5, 64.1, 79.4, 126.7, 128.0, 129.2, 134.0, 137.9, 152.7, 156.5; *m*/*z* (ES$^+$) 372 (16%, MNa$^+$), 350.2144 (31, MH$^+$ $C_{19}H_{32}NO_3Si$ requires 350.2151), 216 (61, MH$^+$-PhMe$_2$Si), 135 (81, PhMe$_2$Si$^+$), 57 (100, ^{t}Bu$^+$).

[1*S*,4*S*]-4-[2-(Dimethylphenylsilanyl)-1-methylallyl]oxazolidin-2-one (18) and [1*S*,4*S*]-4-(1-methylallyl)oxazolidin-2-one (19)

A solution of alcohol **17** (92 mg, 0.27 mmol) in DMSO (1 mL) was treated with a solution of TBAF (0.8 mL of a 1.0 M solution in THF, 0.8 mmol, 3 eq.) and stirred for 30 min. The solution was then heated to 135 °C and stirred for 14 h. The reaction was cooled, quenched with H_2O (1 mL) and extracted into EtOAc (5 mL). The organics were dried ($MgSO_4$) and solvent removed *in vacuo* to furnish the crude product. Purification by flash column chromatography (30% EtOAc–petroleum ether) gave **18** (10.4 mg, 14%) as a colourless oil and the major product **19** (20.1 mg, 53%) as a colourless oil. **18**: ν_{max}(film)/cm^{-1} 3273, 2959, 1755; δ_H (500 MHz; $CDCl_3$) 0.43 (3H, s, Si*M*e$_2$Ph), 0.44 (3H, s, Si*M*e$_2$Ph), 0.90 (3H, d, *J* 6.9, C*H*$_3$CH), 2.42 (1H, dq, *J* 9.0, 6.9, CH$_3$C*H*), 3.73 (1H, q, *J* 8.5, C*H*NH), 4.00 (1H, dd, *J* 8.7, 6.6, C*H*$_2$O), 4.33 (1H, t, *J* 8.5, C*H*$_2$O), 5.06 (1H, br s, N*H*), 5.65 (1H, d, *J* 1.9, C*H*$_2$=C), 5.80 (1H, d, *J* 1.7, C*H*$_2$=C), 7.38–7.39 (3H, m, C*H*$_{Ar}$), 7.50–7.52 (2H, m, C*H*$_{Ar}$); δ_C (125 MHz; $CDCl_3$) − 2.8, −2.6, 16.7, 44.1, 56.0, 68.7, 127.9, 128.2, 129.6, 133.9, 137.2, 152.5, 159.0; *m*/*z* (EI$^+$) 275.1342 (1%, M$^+$ $C_{15}H_{21}NO_2Si$ requires 275.1322), 260 (68, M$^+$-CH$_3$), 135 (100, PhMe$_2$Si$^+$). **19**: ν_{max}(film)/cm^{-1} 3286, 2970, 2920, 1748; δ_H (400 MHz; $CDCl_3$) 1.02 (3H, d, *J* 6.8, C*H*$_3$CH), 2.28 (1H, sext, *J* 7.2, CH$_3$C*H*), 3.69 (1H, q, *J* 7.8, C*H*NH), 4.14 (1H, dd, *J* 8.8, 6.1, C*H*$_2$O), 4.46 (1H, t, *J* 8.6, C*H*$_2$O), 5.16 (1H, d, *J* 10.5, C*H*$_2$=CH), 5.17 (1H, dt, *J* 17.4, 1.2), 5.65 (1H, ddd, *J* 16.9, 10.6, 8.1, CH$_2$=C*H*), 5.67 (1H, br.s, N*H*); δ_C (100 MHz; $CDCl_3$) 15.4, 42.9, 56.4, 68.3, 117.7, 138.4, 159.3; *m*/*z* (EI$^+$) 141.0793 (4%, M$^+$ $C_7H_{11}NO_2$ requires 141.0790), 86 (100, M$^+$–C_4H_7).

[4*S*]-4-((*S*)-*sec*-Butyloxazolidin-2-one (20)

A solution of oxazolidinone **19** (20.1 mg, 0.143 mmol) in EtOAc (1 mL) was treated with PtO_2 (5.0 mg, 22 μmol, 15 mol%) and stirred under a positive atmosphere of H_2 (balloon) for 4 h. The reaction was filtered through a plug of cotton wool, and the solvent was removed *in vacuo* to give **20** (20.1 mg, 98%) as a clear oil; $[\alpha]_D$ + 1.6 (*c* 1.3 in $CHCl_3$) [lit[30] $[\alpha]_D$ + 2.6 (*c* 1.3 $CHCl_3$)]; δ_H (400 MHz; $CDCl_3$) 0.88 (3H, d, *J* 6.8, C*H*$_3$CH), 0.93 (3H, t, *J* 7.4, C*H*$_3$CH$_2$), 1.15 (1H, m, C*H*$_2$CH$_3$), 1.53 (2H, m, C*H*CH$_3$ + C*H*$_2$CH$_3$), 3.70 (1H, q, *J* 6.9, C*H*NH), 4.11 (1H, dd, *J* 8.6, 6.5, C*H*$_2$O), 4.46 (1H, t, *J* 8.6, C*H*$_2$O), 6.22 (1H, br s, N*H*). All other spectral data were in agreement with literature.[30]

[2*S*,3*R*]-2-*N*-Boc-amino-4-(dimethylphenylsilanyl)-3-methylpent-4-enoic acid (10)

To a solution of alcohol **17** (90 mg, 0.26 mmol) in CH_2Cl_2 (1.1 mL) was added Dess–Martin periodinane (120 mg, 0.28 mmol, 1.1 eq.) and the reaction stirred at rt. After 2 h the reaction was partitioned between saturated aq. $NaHCO_3$ (5 mL) and Et_2O (15 mL), separated and the aqueous re-extracted with Et_2O (15 mL). The combined organics were washed with saturated aq. $NaHCO_3$ (10 mL), dried ($MgSO_4$) and the solvents removed *in vacuo* to leave the aldehyde as a cloudy oil. The crude aldehyde was then dissolved in ^{t}BuOH (6.3 mL), pH 4 buffer solution (1.7 mL), and 2-methyl-2-butene (2 M in THF, 1.3 mL). The resulting pink solution was treated with NaO_2Cl (29 mg, 0.33 mmol, 1.25 eq.) and the solution stirred for 2 h, during which time the solution became yellow. The reaction was diluted with water (10 mL) and Et_2O (10 mL) and separated. The aqueous was re-extracted with Et_2O (5 mL) and the combined organics dried ($MgSO_4$) and the solvents removed *in vacuo* to give a cloudy oil. Purification by flash column chromatography (1% AcOH, 49% EtOAc–petroleum ether) gave (+)-**10** (65 mg, 69% over 2 steps) as a colourless oil; δ_H (400 MHz; $CDCl_3$) 0.43 (6H, s, Si*M*e$_2$), 1.05 (3H, d, *J* 6.9, C*H*$_3$CH), 1.44 (9H, s, *Boc*), 2.64 (1H, m, C*H*CH$_3$), 4.18 (1H, t, *J* 8.2, NHC*H*), 4.62 (1H, d, *J* 7.8, N*H*), 5.60 (1H, d, *J* 1.6, C=C*H*$_2$), 5.81 (1H, br s, C=C*H*$_2$), 7.37–7.39 (3H, m, C*H*$_{Ar}$), 7.54–7.57 (2H, m, C*H*$_{Ar}$). All other spectral data were in agreement with literature.[2]

[1-Dimethylcarbamoyl-3-(dimethylphenylsilanyl)-2-methylbut-3-enyl]carbamic acid *tert*-butyl ester (34)

A commercially available solution of $HNMe_2$ (2.0 M in THF) was cooled to −190 °C and a stream of N_2 passed over it into a flame-dried flask, cooled to −78 °C, *via* cannula. The frozen liquid was slowly allowed to warm to rt with a continuous flow of N_2 passing any vapour through to the second flask. This process was continued until the smell of amine ceased from the former flask. The now concentrated solution of amine was maintained at −78 °C until required. A solution of acid (+)-**10** (65 mg, 0.18 mmol) in CH_2Cl_2 (1 mL) was cooled to −30 °C and HOBt (27 mg, 0.20 mmol, 1.1 eq.) and DCC (41 mg, 0.20 mmol, 1.1 eq.) were added. This solution was then treated with dimethylamine (1 mL of concentrated solution from above) and allowed to warm to rt over 2 h. The excess amine and solvent were removed *in vacuo* and replaced with EtOAc (10 mL). The resultant suspension was filtered *via* Celite® and the solvent removed *in vacuo* to furnish the crude product as a cloudy suspension. Purification by flash column chromatography (30% EtOAc– petroleum ether) gave **34** (54 mg, 78%) as a colourless oil; $[\alpha]_D$ + 26.4 (*c* 2.7 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.44 (3H, s, Si*M*e$_2$), 0.46 (3H, s, Si*M*e$_2$), 0.90 (3H, d, *J* 7.0, C*H*$_3$CH), 1.41 (9H, s, *Boc*), 2.66 (1H, m, C*H*CH$_3$), 2.92 (3H, s, N*Me*$_2$), 3.10 (3H, s, N*Me*$_2$), 4.62 (1H, t, *J* 9.4, NHC*H*), 4.77 (1H, d, *J* 9.0, N*H*), 5.62 (1H, d, *J* 2.3, C=C*H*$_2$), 5.85 (1H, d, *J* 1.6, C=C*H*$_2$), 7.34–7.37 (3H, m, C*H*$_{Ar}$), 7.54–7.57 (2H, m, C*H*$_{Ar}$); δ_C (100 MHz; $CDCl_3$) − 2.1, −2.0, 14.5, 18.8, 28.8, 36.1, 37.9, 43.4, 53.2, 79.6, 128.3, 128.5, 129.5, 134.6, 151.7, 155.2, 172.9. All other spectral data were in agreement with literature.[2]

[*N*-Boc-[5-*tert*-butoxy-2-(dimethylphenylsilanyl)-pent-2-enyl]amino]acetic acid methyl ester (39)

To a suspension of KH (1.70 g of a 30% suspension in mineral oil, washed twice with petroleum ether, 12.7 mmol, 1.26 eq.) in THF (50 mL) at 0 °C, Boc–Gly–OMe (2.00 g, 10.6 mmol, 1.05 eq.) was added dropwise, and the resultant yellow suspension stirred for 1 h. Bromide **38**[1c] was then added dropwise, the resultant solution then warmed to rt over 3 h and stirred for 14 h, by which point the solution had turned red. The reaction was cautiously quenched with saturated aq. $NaHCO_3$ (30 mL), diluted with Et_2O (50 mL) and separated. The aqueous layer was re-extracted with Et_2O (30 mL) and the combined organics washed with brine (30 mL) and then dried ($MgSO_4$) before the solvents were removed *in vacuo*. Purification by flash column chromatography (10% EtOAc–petroleum ether) gave **39** (4.19 g, 90%) as a colourless oil; ν_{max}(film)/cm^{-1} 3069, 3006, 2955, 2870, 1748, 1694; δ_H (400 MHz; $CDCl_3$) 0.41 (6H, s, Si*M*e$_2$), 1.11 (9H, s, CH$_2$O^t*Bu*), 1.43 (9H, m, *Boc*), 2.24–2.29

(2H, m, $CH_2CH_2O^tBu$), 3.20 (2H, m, $CH_2CH_2O^tBu$), 3.70 (3H, s, O*Me*), 3.70 (1H, s, NCH_2), 3.87 (1H, s, NCH_2), 4.03 (1H, s, NCH_2), 4.09 (1H, s, NCH_2), 6.06–6.14 (1H, m, C=C*H*), 7.33–7.34 (3H, m, CH_{Ar}), 7.49–7.52 (2H, m, CH_{Ar}); δ_C (100 MHz; $CDCl_3$) −1.4, −1.3, 27.5, 28.3, 33.3, 46.3, 46.5, 51.8, 54.3, 54.6, 60.9, 72.6, 80.1, 80.3, 127.9, 128.9, 129.0, 133.7, 133.9, 134.4, 138.8, 139.0, 143.7, 145.0, 155.1, 155.9, 170.7, 170.8; *m/z* (FAB) 486 (4%, MNa^+), 464 (7, MH^+), 463.2740 (M^+ $C_{25}H_{41}NO_5Si$ requires 463.2754), 386 (4, MNa^+-Boc), 364 (10, MH^+-Boc), 330 (18, MH^+-$PhMe_2Si$), 135 (75, $PhMe_2Si^+$), 57 (100, $^tBu^+$).

[*N*-Boc-[5-*tert*-butoxy-2-(dimethylphenylsilanyl)-pent-2-enyl]-amino]-acetic acid

A solution of NaOH (340 mg, 8.5 mmol, 3.5 eq.) in H_2O (5.5 mL) was added to a solution of **39** (1.13 g, 2.43 mmol) in THF (5.5 mL) at rt and was stirred for 23 h. The reaction was acidified with citric acid to pH 3, diluted with Et_2O (10 mL) and then separated. The aqueous was re-extracted with Et_2O (10 mL) and the combined organics dried ($MgSO_4$) before the solvents were removed *in vacuo* to give the acid (1.08 g, 99%) as a colourless oil, which was used without further purification; ν_{max}(film)/cm^{-1} 2974, 2930, 2871, 1726, 1694 (C=O_{Boc}); δ_H (400 MHz, DMSO, 95 °C) 0.40 (6H, s, SiMe_2), 1.09 (9H, s, CH_2O^tBu), 1.41 (9H, s, *Boc*), 2.17 (2H, q, *J* 6.9, $CH_2CH_2O^tBu$), 3.22 (2H, t, *J* 6.7, $CH_2CH_2O^tBu$), 3.58 (2H, br s, NCH_2), 3.98 (2H, br s, NCH_2), 6.07 (1H, t, *J* 7.3, C=C*H*), 7.34–7.36 (3H, m, CH_{Ar}), 7.51–7.53 (2H, m, CH_{Ar}); δ_C (100 MHz, DMSO-d6, 95 °C) −0.5, 28.2, 29.0, 33.8, 49.1, 53.9, 61.5, 72.8, 79.1, 128.5, 129.6, 134.3, 138.2, 139.8, 156.0, 175.7; *m/z* (FAB) 472.2519 (5%, MNa^+ $C_{24}H_{39}NNaO_5Si$ requires 472.2495), 135 (37, $PhMe_2Si^+$), 57 (100, $^tBu^+$).

[*N*-Boc-[5-*tert*-butoxy-2-(dimethylphenylsilanyl)pent-2-enyl]amino]acetic acid [1*R*,2*S*,5*R*]-8-phenylmenthol ester (37)

A solution of the acid derived from **39** (2.73 g, 6.07 mmol, 1.05 eq.) in CH_2Cl_2 (30 mL) was cooled to −30 °C and treated sequentially with DCC (1.79 g, 8.67 mmol, 1.5 eq.), DMAP (70 mg, 0.58 mmol, 0.1 eq.) and (−)-8-phenyl menthol (1.34 g, 5.78 mmol, 1 eq.). The resultant solution was allowed to warm to rt over 14 h, by which point the solution had turned yellow. The solvent was removed *in vacuo* and replaced with EtOAc (40 mL). Filtration through Celite® and evaporation of the solvent *in vacuo* afforded the crude product, which was purified by flash column chromatography (8% EtOAc–petroleum ether) to give **37** (2.75 g, 72%) as a thick colourless oil; $[\alpha]_D$ − 2.2 (*c* 0.6 in $CHCl_3$); ν_{max}(film)/cm^{-1} 2972, 2925, 2869, 1744, 1701 (C=O_{Boc}); δ_H (400 MHz, $CDCl_3$) 0.44 (3H, s, SiMe_2), 0.45 (3H, s, SiMe_2), 0.89 (3H, d, *J* 2.8, CHCH_3), 1.14 (9H, s, CH_2O^tBu), 1.26 (3H, s, C(Ph)Me_2), 1.33 (3H, s, C(Ph)Me_2), 1.45 (9H, m, *Boc*), 0.83–1.64 (6H, m, C*H*CH_3 + $CH(CH_3)CH_2CH_2$ + $CH(CH_3)CH_2CH_2$ + C*H*CMe_2Ph), 1.96–2.01 (2H, m, $CH_2CH(C)OR$), 2.29–2.31 (2H, m, $CH_2CH_2O^tBu$), 3.22 (2H, t, *J* 6.9, $CH_2CH_2O^tBu$), 3.26–3.63 (2H, m, NCH_2), 3.94–4.16 (2H, m, NCH_2), 4.83–4.91 (1H, m, CO_2CH), 6.01 (1H, t, *J* 7.1, C=$CH_{minor\ rot.}$), 6.08 (1H, t, *J* 7.3, C=$CH_{major\ rot.}$), 7.12–7.16 (1H, m, CH_{Ar}), 7.26–7.29 (4H, m, CH_{Ar}), 7.36–7.37 (3H, m, CH_{Ar}), 7.53–7.55 (2H, m, CH_{Ar}); δ_C (100 MHz, $CDCl_3$) −1.5, −1.4, −1.3, 21.8, 26.4, 26.8, 26.9, 27.5, 28.3, 31.3, 33.3, 34.5, 34.9, 39.9, 41.8, 41.9, 46.8, 47.2, 50.4, 50.5, 54.1, 54.3, 60.9, 72.6, 75.2, 79.9, 125.1, 125.2, 125.4, 127.5, 127.8, 127.9, 128.9, 133.7, 134.2, 138.7, 139.0, 141.4, 143.2, 151.2, 155.2, 155.7, 169.3; *m/z* (FAB) 687 (3%, MNa^+), 664.4375 (4, MH^+ $C_{40}H_{62}NO_5Si$ requires 664.4397), 135 (45, $PhMe_2Si^+$), 105 (100, $PhSi^+$), 119 (67, $PhSiMe^+$), 57 (75, $^tBu^+$).

[2*S*,3*R*]-2-*N*-Boc-amino-3-(2-*tert*butoxyethyl)-4-(dimethylphenylsilanyl)pent-4-enoic acid [1*R*,2*S*,5*R*]-8-phenylmenthol ester (40)

Rearrangement precursor **37** (95 mg, 0.14 mmol) in anhydrous PhMe (1 mL) was transferred into a flame dried flask and the solvent removed *in vacuo*. The residue was redissolved in THF (1 mL) and 18-C-6 (37 mg, 0.14 mmol, 1.0 eq.) was added. This solution was then added to KH (47 mg of a *ca.* 30% weight solution in mineral oil, washed with dry petroleum ether, 2.5 eq.) in THF (0.5 mL) at 0 °C *via* cannula over 5 min. The resultant suspension was stirred at rt for 3 h before being cautiously quenched with saturated aq. NH_4Cl (1 mL), and stirred for 5 min. The biphasic solution was partitioned between Et_2O (5 mL) and H_2O (5 mL), the organics separated, dried ($MgSO_4$) and the solvents removed *in vacuo*. The crude product was purified twice by flash column chromatography (Biotage®, 8% EtOAc–petroleum ether) to give **40** (45 mg, 47%) as a colourless oil; $[\alpha]_D$ + 1.9 (*c* 1.2 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3437, 2954, 2927, 2872, 1713; δ_H (400 MHz, $CDCl_3$) 0.42 (3H, s, SiMe_2), 0.43 (3H, s, SiMe_2), 0.73–1.73 (8H, m, $CH_2CH(C)OR$ + $CH(CH_3)CH_2CH_2$ + $CH(CH_3)CH_2CH_2$ +$CH_2CH_2O^tBu$), 0.83 (3H, d, *J* 6.5, CHCH_3), 1.10 (9H, s, CH_2O^tBu), 1.26 (3H, s, C(Ph)Me_2), 1.33 (3H, s, C(Ph)Me_2), 1.44 (9H, s, *Boc*), 1.87–1.96 (2H, m, C*H*CH_3 + C*H*CMe_2Ph), 2.55–2.66 (1H, m, C*H*C=CH_2), 2.92–3.02 (1H, m, $CH_2CH_2O^tBu$), 3.10–3.16 (1H, m, $CH_2CH_2O^tBu$), 3.94 (1H, t, *J* 8.4, NHC(C)*H*CO_2R), 4.70–4.78 (1H, m, N*H* + CO_2CH), 5.57 (1H, d, *J* 1.9, C=CH_2), 5.75 (1H, d, *J* 1.3, C=CH_2), 7.20–7.55 (10H, m, CH_{Ar}); δ_C (100 MHz, $CDCl_3$) −2.0, −1.7, 21.8, 25.8, 27.1, 27.6, 28.1, 28.4, 29.8, 31.4, 31.9, 34.6, 40.1, 41.7, 45.2, 50.7, 56.8, 59.4, 72.6, 76.3, 79.3, 125.4, 125.8, 127.9, 128.1, 129.2, 130.2, 134.2, 138.2, 149.2, 150.8, 154.9, 171.6; *m/z* (ES^+) 687 (38%, MNa^+), 664.4337 (100, MH^+ $C_{40}H_{62}NO_5Si$ required 664.4397), 564 (69, MH^+-Boc).

[1*S*,2*R*]-[2-(2-*tert*-Butoxyethyl)-3-(dimethylphenylsilanyl)-1-hydroxymethylbut-3-enyl]carbamic acid *tert*-butyl ester (41)

A suspension of $LiAlH_4$ (54 mg, 1.4 mmol, 3 eq.) in Et_2O (2 mL) was refluxed for 30 min and cooled to 0 °C. A solution of rearrangement product **40** (317 mg, 0.477 mmol) in Et_2O (0.5 mL) was then added *via* cannula, and the resultant suspension stirred at 0 °C for 90 min. The reaction was quenched sequentially with H_2O (54 μL), 15% aq. NaOH (54 μL), and H_2O (162 μL). The resultant suspension was diluted with Et_2O (10 mL), dried ($MgSO_4$) before removal of the solvent *in vacuo*. Purification of the crude product by flash column chromatography (30% EtOAc–petroleum ether) gave **41** (143 mg, 70%) as a colourless oil; $[\alpha]_D$ + 21.5 (*c* 2.0 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3439, 2975, 1701; δ_H (270 MHz, $CDCl_3$) 0.43 (6H, s, SiMe_2), 1.11 (9H, s, CH_2O^tBu), 1.42 (9H, s, *Boc*), 1.57–71 (2H, m, $CH_2CH_2O^tBu$), 2.49 (1H, dt, *J* 7.9, 4.5, CHC=CH_2), 3.02 (1H, dt, *J* 8.2, 6.4, $CH_2CH_2O^tBu$), 3.10–3.25 (2H, m, $CH_2CH_2O^tBu$ + O*H*), 3.51–3.60 (3H, m, CH_2OH + C*H*NH), 4.82 (1H, d, *J* 6.3, N*H*), 5.59 (1H, d, *J* 2.0, C=CH_2), 5.80 (1H, d, *J* 1.9, C=CH_2), 7.32–7.35 (3H, m, CH_{Ar}), 7.51–7.55 (2H, m, CH_{Ar}); δ_C (68 MHz, $CDCl_3$) −2.3, −2.2, 27.4, 28.3, 31.8, 55.1, 59.8, 63.6, 73.0, 79.1, 127.8, 129.1, 129.2, 133.9, 137.9, 151.4, 156.1; *m/z* (ES^+) 458.2735 (78%, MNa^+ $C_{24}H_{41}NO_4SiNa$ required 458.2703), 436 (34, MH^+), 336 (77, MH^+-Boc).

[2*S*,3*R*]-2-*N*-Boc-amino-3-(2-*tert*-butoxyethyl)-4-(dimethylphenylsilanyl)pent-4-enoic acid (42)

To a solution of alcohol **41** (54 mg, 0.13 mmol) in CH_2Cl_2 (0.5 mL) was added Dess–Martin periodinane (60 mg, 0.14 mmol, 1.1 eq.). The reaction was stirred at rt for 14 h before saturated aq. $NaHCO_3$ (2 mL) was added. The mixture was diluted with Et_2O (10 mL), separated and the aqueous layer re-extracted with Et_2O (10 mL). The combined organics washed with saturated aq. $NaHCO_3$ (10 mL), dried ($MgSO_4$) and solvents removed *in vacuo* to leave the aldehyde as a cloudy oil (51 mg, 92%). The crude aldehyde was then dissolved in ^tBuOH (3 mL), pH 4 buffer solution (0.8 mL), and 2-methyl-2-butene (2 M in THF, 0.6 mL). The resultant pink solution was treated with NaO_2Cl (13 mg, 0.148 mmol, 1.25 eq.) and the solution stirred for 2 h during which time the solution became

yellow. The reaction was diluted with water (5 mL) and Et_2O (5 mL) and separated. The aqueous layer was re-extracted with Et_2O (5 mL), the combined organics were dried ($MgSO_4$) and the solvents then removed *in vacuo* to furnish the product as a cloudy oil. Purification by flash column chromatography (1% AcOH, 19% EtOAc–petroleum ether) gave **42** (43 mg, 75% over 2 steps) as a colourless oil; $[\alpha]_D$ + 39.5 (*c* 1.1 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3444, 3324, 2975, 1716, 1667; δ_H (400 MHz, $CDCl_3$): 0.46 (6H, s, Si*Me*$_2$), 1.14 (9H, s, CH_2O^tBu), 1.44 (9H, s, *Boc*), 1.59–1.64 (1H, m, $CH_2CH_2O^tBu$), 1.76–1.83 (1H, m, $CH_2CH_2O^tBu$), 2.70–2.75 (1H, m, $CHC{=}CH_2$), 3.20–3.26 (1H, m, $CH_2CH_2O^tBu$), 3.39–3.44 (1H, m, $CH_2CH_2O^tBu$), 4.48 (1H, t, *J* 8.8, NHC*H*), 4.88 (1H, d, *J* 8.8, N*H*), 5.75 (1H, d, *J* 1.7, C=CH_2), 5.92 (1H, br s, C=CH_2), 7.36–7.39 (3H, m, CH_{Ar}), 7.51–7.53 (2H, m, CH_{Ar}); δ_C (100 MHz, $CDCl_3$): −2.6, 20.8, 27.5, 28.4, 30.8, 44.0, 55.9, 57.5, 58.7, 74.5, 79.8, 128.0, 129.4, 129.9, 134.0, 137.4, 148.1, 155.4, 175.3, 176.7; MS (ES$^+$): *m*/*z* 472.2495 (21%, MNa$^+$ $C_{24}H_{39}NO_5SiNa$ required 458.2496).

[2*S*.3*R*]-[2-(2-*tert*-Butoxyethyl)-1-dimethylcarbamoyl-3-(dimethylphenylsilanyl)but-3-enyl]carbamic acid *tert*-butyl ester (36)

In an identical procedure to the preparation of **34**, acid **42** (25 mg, 55 μmol) in CH_2Cl_2 (0.25 mL) was treated with HOBt (9.0 mg, 66 μmol, 1.1 eq.), DCC (14 mg, 66 μmol, 1.1 eq.) and concentrated Me_2NH solution in THF (1 mL). The crude product was isolated as a cloudy suspension. The product was dissolved in hexane (2 mL), filtered, and evaporated to leave the product as a cloudy oil, which solidified on standing to a white solid (20 mg, 76%); mp 102–104 °C (lit.,[1c] 104–6 °C); $[\alpha]_D$ + 18.2 (*c* 1.0 in $CHCl_3$); δ_H (270 MHz, $CDCl_3$): 0.44 (6H, s, Si*Me*$_2$), 1.07 (9H, s, CH_2O^tBu), 1.41 (9H, s, *Boc*), 1.51–1.61 (2H, m, $CH_2CH_2O^tBu$), 2.67–2.71 (1H, m, $CHC{=}CH_2$), 2.90 (3H, s, N*Me*$_2$), 2.97–3.03 (1H, m, $CH_2CH_2O^tBu$), 3.01 (3H, s, N*Me*$_2$), 3.10–3.15 (1H, m, $CH_2CH_2O^tBu$), 4.55 (1H, t, *J* 8.9, NHC*H*), 4.93 (1H, d, *J* 8.9, N*H*), 5.63 (1H, d, *J* 1.6, C=CH_2), 5.86 (1H, d, *J* 1.9, C=CH_2), 7.34–7.37 (3H, m, CH_{Ar}), 7.55–7.59 (2H, m, CH_{Ar}); *m*/*z* (ES$^+$) 477.3155 (100, MH$^+$ $C_{26}H_{45}N_2O_4Si$ required 477.3149). Spectroscopic and analytical data were identical to that recorded in the literature.[1c]

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References

1 (*a*) J. C. Anderson and A. Flaherty, *J. Chem. Soc., Perkin Trans. 1*, 2001, 267; (*b*) J. C. Anderson and S. Skerratt, *J. Chem. Soc., Perkin Trans. 1*, 2002, 2871–9; (*c*) J. C. Anderson and M. Whiting, *J. Org. Chem.*, 2003, **68**, 6160–3.
2 J. C. Anderson, A. Flaherty and M. E. Swarbrick, *J. Org. Chem.*, 2000, **65**, 9152, and references therein.
3 (*a*) N. Sayo, K. Azuma, K. Mikami and T. Nakai, *Tetrahedron Lett.*, 1984, **25**, 565; (*b*) N. Sayo, F. Shirai and T. Nakai, *Chem. Lett.*, 1984, 255; (*c*) N. Sayo, E.-I. Kitahara and T. Nakai, *Chem. Lett.*, 1984, 259; (*d*) T. Nakai and K. Mikami, *Org. React.*, 1994, **46**, 105; (*e*) D. J.-S. Tsai and M. M. Midland, *J. Org. Chem.*, 1984, **49**, 1843.
4 (*a*) K. Mikami, K. Fujimoto, T. Kasuga and T. Nakai, *Tetrahedron Lett.*, 1984, **25**, 6011; (*b*) K. Mikami, T. Kasuga, K. Fujimoto and T. Nakai, *Tetrahedron Lett.*, 1986, **27**, 4185; (*c*) O. Takahashi, K. Mikami and T. Nakai, *Chem. Lett.*, 1987, **1**, 69.
5 (*a*) E. Nakai and T. Nakai, *Tetrahedron Lett.*, 1988, **29**, 4587; (*b*) R. Brückner, *Chem. Ber.*, 1989, **122**, 193.
6 J. A. Marshall and J. Lebreton, *J. Am. Chem. Soc.*, 1988, **110**, 2925.
7 K. Fujimoto and T. Nakai, *Tetrahedron Lett.*, 1994, **35**, 5019.
8 (*a*) J. Åhman and P. Somfai, *J. Am. Chem. Soc.*, 1994, **116**, 9781; (*b*) J. Åhman, T. Jarevång and P. Somfai, *J. Org. Chem.*, 1996, **61**, 8148, and references therein.
9 (*a*) I. Coldham, A. J. Collis, R. J. Mould and R. E. Rathmell, *Tetrahedron Lett.*, 1995, **36**, 3557; (*b*) I. Coldham, A. J. Collis, R. J. Mould and R. E. Rathmell, *J. Chem. Soc., Perkin Trans. 1*, 1995, 2739.
10 R. E. Gawley, Q. Zhang and S. Campagna, *J. Am. Chem. Soc.*, 1995, **117**, 11817.
11 (*a*) E. K. Verner and T. Cohen, *J. Am. Chem. Soc.*, 1992, **114**, 375; (*b*) R. Hoffmann and R. Brückner, *Angew. Chem., Int. Ed.*, 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. (Tokyo)*, 1995, **53**, 480.
12 (*a*) J. A. Marshall and X.-J. Wang, *J. Org. Chem.*, 1992, **57**, 2747; (*b*) S. Manabe, *Chem. Commun.*, 1997, 737.
13 (*a*) P. Beak and S. T. Kerrick, *J. Am. Chem. Soc.*, 1991, **113**, 9708; (*b*) P. Beak, S. T. Kerrick, S. Wu and J. Chu, *J. Am. Chem. Soc.*, 1994, **116**, 3231.
14 N. C. Faibish, Y. S. Park, S. Lee and P. Beak, *J. Am. Chem. Soc.*, 1997, **119**, 11561.
15 D. C. Siddons, PhD thesis, University of Sheffield, 1998.
16 J. C. Anderson and S. Anguille, unpublished results.
17 (*a*) Y. S. Park, M. L. Boys and P. Beak, *J. Am. Chem. Soc.*, 1996, **118**, 3757; (*b*) S. Wu, S. Lee and P. Beak, *J. Am. Chem. Soc.*, 1996, **118**, 715; (*c*) M. Schlosser and D. Limat, *J. Am. Chem. Soc.*, 1995, **117**, 12342; (*d*) C. Barberis, N. Voyer, J. Roby, S. Chénard, M. Tremblay and P. Labrie, *Tetrahedron*, 2001, **57**, 2065; (*e*) J. Clayden, C. J. Menet and D. J. Mansfield, *Chem. Commun.*, 2002, 38.
18 P. O'Brien, *J. Chem. Soc., Perkin Trans. 1*, 1998, 1439.
19 M. Furukawa and T. Okawara, *J. Chem. Soc., Chem. Commun.*, 1976, 339.
20 J. C. Anderson, D. C. Siddons, S. C. Smith and M. E. Swarbrick, *J. Chem. Soc., Chem. Commun.*, 1995, 1835.
21 A. I. Meyers, D. L. Temple, R. L. Nolen and E. D. Mihelich, *J. Org. Chem.*, 1974, **39**, 2778, and references therein.
22 The mixture containing acid **10** was esterified with diazomethane to give a mixture containing methyl esters **11** (83%) in order to aid purification and verify the stereochemical assignment to the identical ester prepared previously, ref. 2 and M. E. Swarbrick, PhD thesis, University of Sheffield, 1997.
23 Cited in the literature, but no synthesis: D. P. G. Hamon, R. A. Massy-Westropp and P. Razzino, *Tetrahedron*, 1992, **48**, 5163.
24 Synthesised in >99.5% optical purity in 5 steps from technical grade (+)-pulegone: O. Ort, *Org. Synth.*, 1987, **65**, 203.
25 Diastereomeric ratio determined from alkene region of ^{1}H NMR spectrum: **14**; δ 5.50 (1H, s) and 5.74 (1H, s), *versus* **15**; δ 5.55 (1H, d, *J* 1.9) and 5.80 (1H, s).
26 This has been noted before: T. J. Donohoe, P. M. Guyo and M. Helliwell, *Tetrahedron Lett.*, 1999, **40**, 435.
27 V. M. Mićović and M. L. Mihailović, *J. Org. Chem.*, 1953, **18**, 1190.
28 J. C. Anderson, S. C. Smith and M. E. Swarbrick, *J. Chem. Soc., Perkin Trans. 1*, 1997, 1517.
29 H. Oda, M. Sato, Y. Morizawa, K. Oshima and H. Nozaki, *Tetrahedron*, 1985, **41**, 3257.
30 N. Lewis, A. McKillop, R. J. K. Taylor and R. J. Watson, *Synth. Commun.*, 1995, **24**, 561.
31 Astec BDM column (20 m × 250 μm), T = 180 °C, R_t (2*R*, 3*R*)-**20**; 19.3 min, (2*S*, 3*S*)-**20**; 20.5 min.
32 J. Seyden Penne, *Chiral Auxiliaries and Ligands in Asymmetric Synthesis*, John Wiley and Sons, New York, 1995.
33 (*a*) A. G. Myers, B. H. Yang, H. Chen, L. McKinstry, D. J. Kopecky and J. L. Gleason, *J. Am. Chem. Soc.*, 1997, **119**, 6496; (*b*) A. G. Myers and L. J. McKinstry, *J. Org. Chem.*, 1996, **61**, 2428.
34 D. Yang, M. Xu and M.-Y. Bian, *Org. Lett.*, 2001, **3**, 111.
35 G.-B. Huang, K.-M. Wu and L. Huang, *Gaodeng Xuexiao Huaxue Xuebao*, 1999, **20**, 1394.
36 J. I. Levin, E. Turos and S. M. Weinreb, *Synth. Commun.*, 1982, **12**, 989.
37 Synthesised in >99.5% optical purity in 5 steps from technical grade (+)-pulegone: O. Ort, *Org. Synth.*, 1987, **65**, 203.
38 J. C. Anderson, R. M. Denton and C. Wilson, *Org. Lett.*, 2005, **7**, 123.
39 J. C. Anderson, D. C. Siddons, S. C. Smith and M. E. Swarbrick, *J. Org. Chem.*, 1996, **61**, 4820.
40 From the condensation of Boc-glycine and 2-amino-2-methylpropan-1-ol in xylenes, Dean–Stark for 14 h, 65%. L. N. Pridgen and G. Miller, *J. Heterocycl. Chem.*, 1986, **51**, 5291.