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Diastereoselective synthesis of substituted prolines via 5-*endo-trig* cyclisations of aza-[2,3]-Wittig sigmatropic rearrangement products

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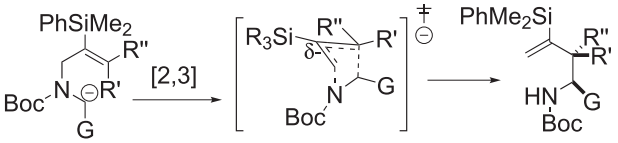
ABSTRACT

The major diastereoisomers of aza-[2,3]-Wittig sigmatropic rearrangement products from α-amino acid derivatives are susceptible to a rare nucleophilic 5-*endo-trig* cyclisations of an amine onto a non-conjugated vinylsilane in high yield and complete diastereocontrol. Five examples are presented, with cyclisation yields between 35 and 87%. A rationale for the stereoselectivity of the cyclisation is forwarded based upon the steric control factors that have been documented for the aza-[2,3]-Wittig sigmatropic rearrangement. A discussion of the mechanism in the context of the reaction conditions is also presented. Oxidation of the silyl group to a hydroxyl group and complete removal were demonstrated for synthetic utility.

1. Introduction

We have developed the aza-[2,3]-Wittig sigmatropic rearrangement as a synthetic method for the synthesis of unnatural amino acids (Scheme 1).[1] Our work differed from the work of others in the field whose rearrangements relied upon the relief of ring strain inherent to β-lactams[2] and aziridines[3] that resulted in ring expansion products. Despite the efficacy of the [2,3]-Wittig sigmatropic rearrangement for acyclic allylic ethers,[3,4] the promotion of the analogous acyclic aza-[2,3]-Wittig sigmatropic rearrangement proved to be considerably more demanding.[5] The calculated small build up of negative charge at the central vinyl carbon atom in the transition states of [2,3]-Wittig rearrangements[6] led us to develop aza-[2,3]-Wittig rearrangement precursors that contained an anion stabilizing dimethylphenylsilyl substituent (Scheme 1). We have defined the limits of activation and, in addition, control of diastereoselectivity imparted by the dimethylphenylsilyl group upon the aza-[2,3]-Wittig sigmatropic rearrangements on acyclic allylic amines[7] and have used this strategy to good effect for the synthesis of naturally occurring amino acids.[8] Conceivably the incorporation of an anion stabilizing group could have rendered the rearrangement non concerted, but in all our previous work we never identified any cyclised products, which may have resulted from protonation of an intermediate α-silyl stabilized carbanion. We have summarised some of our attempted strategies towards preparing enantiomerically pure aza-[2,3]-Wittig rearrangement products and detailed the use of (−)-8 phenylmenthol as a chiral auxiliary.[9] We have also shown that internal chirality transfer can also be effective for the generation of enantiomerically enriched products.[10] In all of these studies the majority of reactions gave high yields of rearrangement product with no evidence of cyclic products being identified.



Scheme 1. R, R′, R″=H, alkyl, Ar; G=carboxylic acid derivative.

We were inspired by Kawabata and Fuji's work, which investigated the asymmetric alkylation of α-amino acids to produce α,α-disubstituted α-amino acid derivatives. The success of this work relies upon the transfer of central chirality to an axially chiral enolate, which is then regenerated as central chirality upon alkylation.[11] An intramolecular example has been developed for the synthesis of prolines (Scheme 2).[11e]

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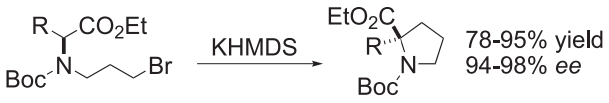
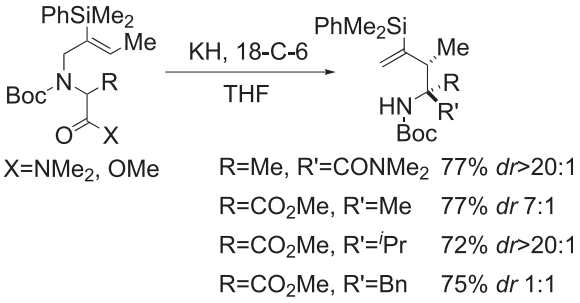


Scheme 2. R=CH_3, ^{i}Pr, Bn, CH_2CH_2SMe, 4-$EtOC_6H_4CH_2$.

We had reported the synthesis of α,α-disubstituted α-amino acid derivatives from the aza-[2,3]-Wittig rearrangement of α-amino acids (Scheme 3).[12] Attempts at also trying to access axially chiral enolates in the initial deprotonation step of enantiomerically pure rearrangement precursors only resulted in racemic products.

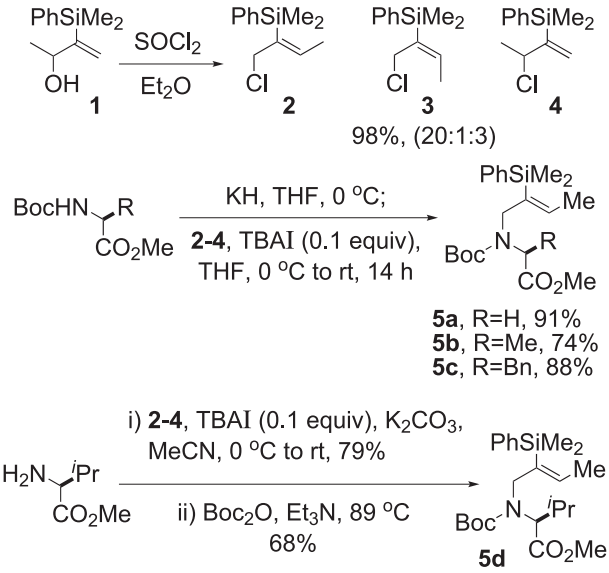


Scheme 3. Synthesis of α,α-disubstituted α-amino acids.

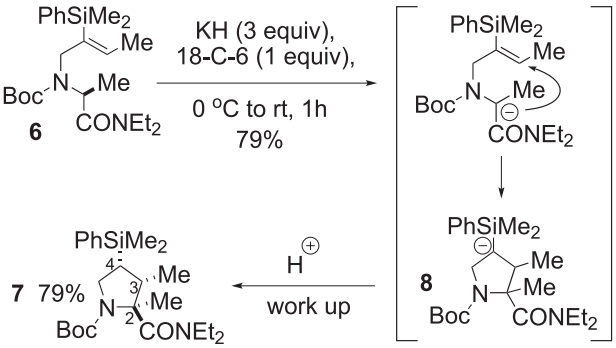
We reinvestigated this research in order to try and find conditions that would enable enantioselective rearrangements via axially chiral enolates.[13] Although this was unsuccessful we were able to characterize an unusual cyclisation reaction that gave densely substituted prolines in diastereomerically defined form.

2. Results and discussion

Our published route to the required rearrangement precursors derived from enantiomerically pure α-amino acids required the use of neat DIBAL for the synthesis of *Z*-1-bromo-2-(phenyldimethylsilyl)-but-3-ene. Problems with the acquisition of neat DIBAL led us to develop an alternative route. Treatment of alcohol **1**[7b] with $SOCl_2$, according to the method of Chan et al.,[14] led to an inseparable mixture of the three allylic chlorides **2**–**4** (20:1:3) in 98% yield (Scheme 4). Determination of the stereochemistry of alkene **2** was by one dimensional NOE experiments. Irradiation of the vinylic proton (δ 6.57, 1H, q, *J*=7.0 Hz) induced an enhancement at CH_2Cl (δ 4.22, 2H, s) and $CHCH_3$ (δ 1.68, 3H, d, *J*=7.1 Hz), which strongly suggested *Z*-stereochemistry. This assignment was supported by irradiation of the minor compound **3** at the vinylic proton (δ 6.19, 1H, q, *J*=6.7 Hz), which induced an enhancement solely at $CHCH_3$ (δ 1.87, 3H, d, *J*=6.8 Hz), suggesting *E*-stereochemistry. The structure of compound **4** was assigned based on the remaining ^{1}H NMR signals. Treatment of the *N*-Boc methyl esters of glycine, alanine and phenylalanine with KH, followed by the mixture of chlorides **2**–**4**, in the presence of catalytic tetra-*n*-butyl ammonium iodide, led to the rearrangement precursors **5a**–**c** in good yields (Scheme 4). The valine analogue **5d** was prepared from alkylation of valine methyl ester with isomeric chlorides **2**–**4** and then Boc protection in refluxing Et_3N. Rearrangement precursors **5a**–**d** were all isolated free from isomeric impurities that could have conceivably arisen from reaction with **3** or **4**. The alanine amide derivative **6** (Scheme 5) was prepared as previously described.[12]



Scheme 4. Synthesis of amino ester rearrangement precursors.



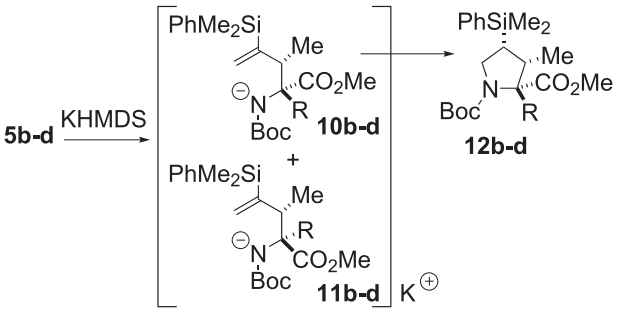
Scheme 5. Formation of proline **7** and postulated mechanism.

We thought that treatment of **6** with KH and 18-C-6 would lead to the aza-[2,3]-Wittig rearranged product,[12] but for the very first time we isolated the cyclised product **7** in 79% yield (Scheme 5). The reaction was monitored closely by TLC and over 1 h only the disappearance of starting material and formation of **7** was observed. Maintaining the reaction at 0 °C for 1 h or longer resulted only in the isolation of starting material. Possibly the proline **7** could be formed from an incomplete rearrangement pathway, where the α-silyl anion intermediate **8** was protonated on work up. However, quenching the reaction with MeOD led to no deuterium incorporation. As KH was used as base the scenario of protonation of **8** from the reaction solvent led us to conduct the experiment in -THF-d_8. Again no deuteration was observed.

The ^{1}H NMR spectrum of **7** showed a number of duplicated peaks, which suggested the presence of diastereoisomers, rotamers or impurities. Removal of the Boc group with 4 M HCl in dioxane gave **9** a single diastereoisomer by crude ^{1}H NMR and was purified to give an oil in 86% yield. The diastereomer depicted (Scheme 5) was verified by one dimensional NOE experiments. Key enhancements were observed upon irradiation of H-3 (δ 2.53, 1H, appt. quintet, *J*=6.6 Hz) at H-4 (6.7%, δ 1.46, 1H, ddd, *J*=11.8, 9.0, 5.9 Hz), which suggested that H-3 and H-4 are on the same face of the proline ring. This interpretation was supported by a 7.0% enhancement for the NOE experiment in the other direction. Irradiation of H-3 also caused an enhancement of the CH_3 groups of the ethyl substituents of the amide group (1.2%, δ 1.46, 6H, t, *J*=7.0 Hz), suggesting that the amide group is also on the

same face as H-3. This was corroborated by an enhancement of the C-2 CH_3 group (1.8%, δ 1.27, 3H, s) upon irradiation of the C-3 CH_3 group (δ 0.93, 3H, d, J=7.2 Hz). In addition previous studies had determined that aza-[2,3]-Wittig rearrangement of **6** gave the 2*S**,3*R** diastereoisomer (dr>20:1, Scheme 1).[12] It therefore seemed probable that this relative stereochemistry was also exhibited in proline **7** (and **8**) and that the C-4 silyl substituent was thus 4*R**. The isolation of a cyclic product from an attempted aza-[2,3]-Wittig rearrangement was an important discovery and prompted us to further investigate the generality of this process and the mechanism of a rare 5-*endo*-*trig* cyclisation.

The amide rearrangement precursor **6**, derived from alanine, was the only α-amino acid that we had found to undergo the aza-[2,3]-Wittig rearrangement in this class of substrate. We had investigated many other base systems to investigate the rearrangement of amide precursors derived from phenyl glycine and valine, and concluded that steric inhibition of resonance prevented deprotonation.[12] No cyclic products were observed in any of these experiments. The analogous methyl ester derivatives rearranged with opposite and varying degrees of diastereoselectivity (Scheme 1). We had shown that the best base systems for aza-[2,3]-Wittig rearrangements were either ^{n}BuLi or LDA in THF/HMPA or DMPU mixtures, or KH, 18-C-6 in THF.[7] We quickly found that for precursors **5b**–**d** treatment with KHMDS in THF/DMPU (4:1), led to efficient cyclisation reactions over prolonged stirring at rt (Scheme 6, and Table 1).



Scheme 6. Cyclisation of amino ester precursors **5b**–**d**.

Aza-[2,3]-Wittig rearrangement of **5b** using KH and 18-C-6 had led to the rearranged products **10b**:**11b** (7:1) in 77% yield (Scheme 1).[12] Treatment with KHMDS with prolonged stirring at rt for 14 h led to the isolation of cyclised material **12b** (41%) and **10b**:**11b** in a reduced diastereomeric ratio of 3:1 in 40% yield. Monitoring of the reaction by TLC revealed the disappearance of starting material to give a spot corresponding to rearranged compounds **10b**:**11b**. This spot then slowly became smaller as another spot corresponding to the cyclised product slowly grew in. This suggested that cyclisation occurs after rearrangement (vide infra). Allowing the reaction to stir for 48 h at rt led to the isolation of the cyclised product **12b** in 68% yield and only 11% of the rearranged products remained **10b**:**11b** with a reversed diastereomeric ratio of 1:10. This suggested that cyclisation of the minor diastereoisomer from the aza-[2,3]-Wittig rearrangement was unfavourable under the reaction conditions. As before, the ^{1}H NMR spectrum of **12b** contained multiple peaks. This was simplified by removing the Boc group with 4 M HCl in dioxane and gave **13b** as a single diastereoisomer by ^{1}H NMR.

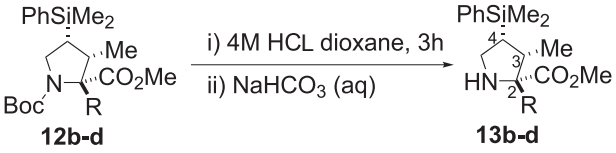
Table 1
[a]Cyclisation and rearrangement of amino ester precursors **5b**–**d**

5	R	*t* (h)	Yield **10** (%)	Yield **11** (%)
b	Me	48	11	68
c	Bn	14	37	35
d	^{i}Pr	48	—	87

[a] KHMDS (2.5 equiv), THF/DMPU (4:1), 0 °C to rt.

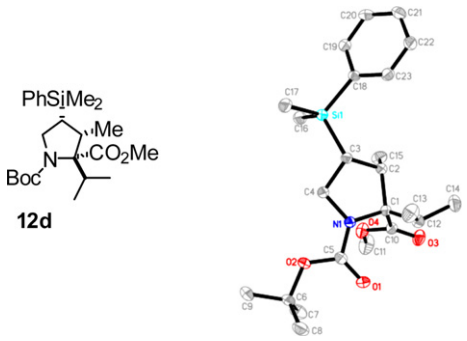
As suitable crystals could not be obtained for X-ray structure determination, one dimensional NOE experiments were conducted in order to verify the stereochemistry at C-4. The relative stereochemistry between C-2 and C-3 had already been established as 2*R**, 3*R**.[12] Irradiation of H-3 (δ 2.81, 1H, app. quintet, J=7.0 Hz) induced an enhancement at H-4 (2.2%, δ 1.80, 1H, ddd, J=11.2, 9.4, 6.4 Hz), which was also detected in the reverse experiment (1.9%). These were similar results to some of the NOE enhancements we had observed for **9**(**7**) and led us to assign the C-4 stereochemistry as 4*R**.

The phenylalanine derivative **5c** had previously been shown to undergo aza-[2,3]-Wittig rearrangement with KH/18-C-6 to give a surprising dr of 1:1 (Scheme 1).[12] Treatment of **5c** with KHMDS and stirring at rt for 14 h led to the isolation of aza-[2,3]-Wittig rearranged product **11c** (37%) and cyclised product **12c** in 35% yield. The relative stereochemistry of **11c** was confirmed by single crystal X-ray structure determination.[13] The ^{1}H NMR of proline **12c** was over complicated again so the Boc group was removed as before (Scheme 7) to give **13c** in 98% yield. Neither of pyrrolidines **12c** or **13c** crystallized so one dimensional NOE experiments were conducted on **13c** to confirm the relative stereochemistry. As before, mutual enhancements between H-3 (3.9%, δ 2.77, 1H, app. quintet, J=6.7 Hz) and H-4 (5.5%, δ 1.55, 1H, ddd, J=11.2, 9.9, 6.2 Hz) confirmed the C-4 stereochemistry as 4*R**. Although we observed an enhancement at CH_2Ph (1.2%, δ 3.12, 1H, d, J=12.8 Hz) upon irradiation of H-3, there was no other NOE data to confirm the stereochemistry of C-2. However, the X-ray data of **11c** had confirmed that the 2*S** diastereisomer had not rearranged, a result consistent with the isolation of **11b**, and suggested that the stereochemistry of **12c** was the depicted 2*R**,3*R**,4*R** diastereoisomer.



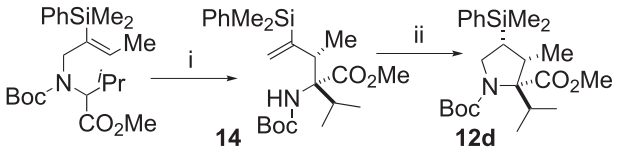
Scheme 7. Boc deprotection.

Treatment of the valine derived precursor **5d** under the cyclisation conditions led to rapid rearrangement by TLC. Prolonged stirring for 48 h at rt led to the exclusive formation of pyrrolidine **12d**. This is in line with the aza-[2,3]-Wittig rearrangement of this substrate (Scheme 1), which is known to proceed with near complete control of diastereoselectivity. The ^{1}H NMR of **12d** was again complicated, but showed only one compound when the Boc group was removed (Scheme 7, 99%). Fortunately suitable crystals of **12d** could be grown and an X-ray structure determination confirmed the relative stereochemistry depicted (Scheme 8).[13] This is consistent with the stereochemical assignment of the rearranged product derived from **5d**,[12] and would again suggest that the major diastereoisomer from the rearrangement of these amino ester derived precursors are prone to cyclisation under these particular reaction conditions. One dimensional NOE experiments on **12d** gave enhancements consistent with this structure (Scheme 8) and corroborated the previous assignments for **12b** and **12c**.



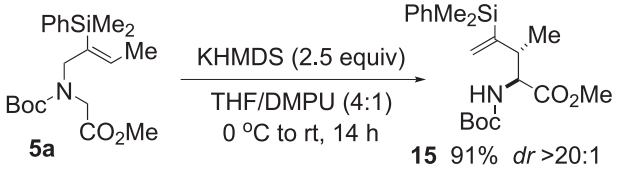
Scheme 8. X-ray structure of **12d**[13].

Conformation that cyclisation proceeded from the rearranged product was provided by treatment of rearrangement product **14** with KHMDS (Scheme 9). This led to the isolation of the corresponding pyrrolidine **12d** in 92% isolated yield.



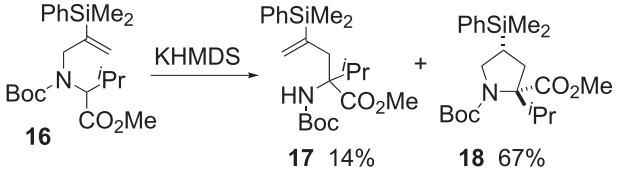
Scheme 9. i) KH, 18-C-6, THF, 0 °C to rt, 72%.[12] (ii) KHMDS, THF/DMPU (4:1), 0 °C to rt, 14 h, 92%.

To determine the importance of the α,α-disubstitution pattern of the precursors with respect to cyclisation, treatment of **5a** with KHMDS under identical conditions led only to the normal rearranged product **15** in 91% yield and dr>20:1 (Scheme 10).[7d] No cyclisation product was observed and highlights the importance of the geminal substitution pattern enhancing cyclisation, possibly due to the Thorpe/Ingold effect.[15]



Scheme 10. Attempted cyclisation of glycine derivative **5a**.

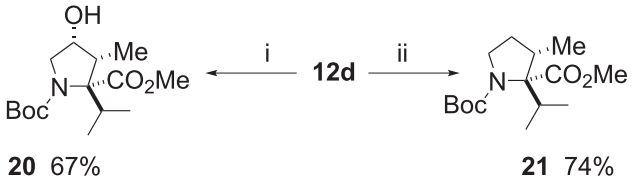
We were also interested to see whether the cyclisation would proceed on a terminal alkene. Treatment of **16** under the cyclisation conditions led to the isolation of the rearranged compound **17** (14%) and the cyclised product **18** (67%) (Scheme 11).



Scheme 11. Cyclisation of terminal alkene substrate.

Removal of the Boc group from **18** in quantitative yield gave a single diastereoisomer **19** by ^{1}H NMR. The reluctance of **18** or **19** to crystallise and no clearly defined single signals in the ^{1}H NMR of **19** made it impossible for the relative stereochemistry between the quaternary centre and the *C*-silyl centre to be determined. By analogy with the previous cyclisations reported in this paper, we tentatively assign the stereochemistry of the pyrrolidine **18** as that depicted.

To show the utility of this cyclisation for the synthesis of substituted proline derivatives we oxidized the phenyldimethylsilyl group with mercury(II) acetate and peracetic acid. Under these conditions alcohol **23** was isolated in 67% yield (Scheme 12).

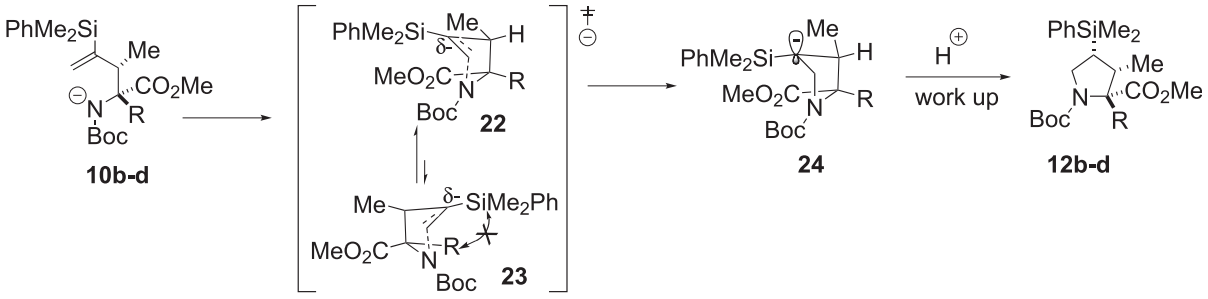


Scheme 12. (i) $Hg(OAc)_2$, AcO_2H (35 wt % in AcOH), 4 h. (ii) TBAF, wet THF, 80 °C, 2 h.

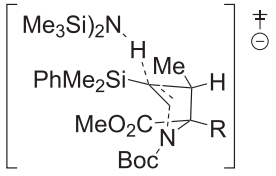
The silicon group had been essential to facilitate and control the diastereoselectivity of the aza-[2,3]-Wittig rearrangement and subsequent cyclisation. Efficient protodesilylation could be achieved by using the conditions of Roush et al.[21] to give **24** in 74% yield.

The results suggest that the cyclisation occurs from the major diastereoisomer of the aza-[2,3]-Wittig rearranged products **10**, but not **11** (Scheme 6). The stereochemical rationale for the aza-[2,3]-Wittig rearrangement we believe is determined by the least pseudo 1,3-diaxial interaction between the phenyldimethylsilyl group and the substituent adjacent to the migrating centre.[7,8,10,12] In the ester series **5b**–**d**, the alkyl group is considered the larger group based upon A-value analysis and gives rise to predominantly isomer **10**.[12] The phenylalanine derivative is an anomalous result, which rearranges with no diastereoselectivity. The major compound **10** can then theoretically cyclise through one of two extreme transitions state structures **22** and **23** (Scheme 13). Presumably the pseudo 1,3-diaxial interaction with the silicon substituent is more demanding than any 1,2 interaction, so transition state structure **22** is favoured, it would seem exclusively, over **23**, leading to intermediate silyl anion **24** Protonation then occurs from the least hindered face of this more reactive conformer leading to the observed stereochemistry for the proline products **12b**–**d**. The rearrangement of amide precursor **6** also fits this stereochemical model. In this system the diethylamide group acts as the larger substituent with respect to the methyl group and controls the diastereoselectivity of the rearrangement and the cyclisation to give **7**. In this rearrangement and like valine precursor **5d** no minor diastereosiomer was detected. The cyclisation of the amide aza-[2,3]-Wittig rearranged product would seem to be particularly fast, so that none of the rearranged product could be detected by TLC. The rate of this particular cyclisation reaction could be enhanced by the amide group increasing the Thorpe/Ingold effect with respect to the ester derivatives.

Deuterium quench studies on the cyclisation of **6** had not revealed any deuteration. Similarly when the cyclisation of **5d** (Scheme 6) was quenched with MeOD, no deuterium incorporation was detected in the pyrrolidine **12d**. These results would suggest that protonation of the developing cyclic intermediate had already occurred. In the experiments using KHMDS an equivalent of hexamethyldisilazane is produced. In the route towards cyclisation the developing α-silyl carbanion could be stabilized and eventually protonated by hexamethyldisilazane (Scheme 14).



Scheme 13. Explanation for diastereoselective cyclisations.



Scheme 14. Possible cyclisation transition state model.

This would render the reaction irreversible if we assume that the KHMDS is then not basic enough to deprotonate α to silicon and facilitate the ring opening process. This mechanism is consistent with our previous observations that under the base systems, which we had previously used for aza-[2,3]-Wittig rearrangement (^{n}BuLi or LDA in THF/HMPA or DMPU mixtures, or KH, 18-C-6 in THF) [7] no cyclisation products had been isolated or detected. Presumably an acidic enough proton is not available for protonation of a developing silicon stabilized carbanion. However, this still does not explain the result of amide precursor **6**, which was rearranged/cyclised with KH and even in THF-d_8 as reaction solvent still didn't give any detectable deuterium incorporation! This result remains an anomaly for future investigation, but it may be possible that this substrate is more prone to cyclisation because of the bulky amide substituent.

This mechanism would constitute a 5-*endo-trig* process, which is normally geometrically disfavoured.[16] However, there have been numerous accounts of the employment of 5-*endo-trig* cyclisations in the synthesis of five-membered rings, suggesting that the process may be more useful than previously considered. Of particular interest to this work is the formation of nitrogen heterocycles via a 5-*endo-trig* cyclisation. This transformation allows for the convenient preparation of the prolific pyrrolidine motif and can be divided into three classes: radical-initiated,[17] electrophile-driven and nucleophile-driven. The nucleophile-driven, anionic 5-*endo-trig* cyclisation of homoallylic amines is less common than its cationic counterpart and usually necessitates the presence of an electron-withdrawing group or a conjugated group in the central vinylic position. For example, Padwa et al. have shown that 5-*endo-trig* cyclisation of vinylsulfones occurs in high yields.[18] Craig et al. have also made use of the 5-*endo-trig* cyclisation of vinylsulfones in their total synthesis of (+)-monomorine I.[19] Pyrrolidine formation via nucleophilic 5-*endo-trig* cyclisation has also been realised with the use of a trifluoromethyl group.[20] The cyclisation was attributed to the highly electrophilic nature of the double bond and the stabilised α-CF_3 carbanion intermediate, both of which are caused by the strong electron-withdrawing ability of the CF_3 group. This demonstrates the nucleophilic 5-*endo-trig* cyclisation of an amine onto a non-conjugated alkene. Although the dimethylphenylsilyl group is not electron-withdrawing, its ability to stabilise α-negative charge must be a contributory factor that allows cyclisation for precursors **6** and **5b**–**d**. In addition the geminal substitution pattern adjacent to the migrating carbanion is also an essential structural motif for rearrangement (compare Scheme 10 with Schemes 6 and 11).

3. Conclusion

The cyclisations **6** to **7** (Scheme 5), **5b**–**d** to **12b**–**d** (Scheme 6) and **16** to **18** (Scheme 11) are rare examples of 5-*endo-trig* cyclisation processes. There is compelling evidence to believe that cyclisation occurs after aza-[2,3]-Wittig sigmatropic rearrangement and that cyclisation occurs from the major, favoured diastereoisomer, suggesting that factors, which have been detailed to control the stereochemistry of the rearrangement are also strongly dominant for the efficacy of the cyclisation reaction. They can be described as nucleophilic 5-*endo-trig* cyclisations of an amine onto a non-conjugated alkene. To the best of our knowledge these represent the first examples of this type of reaction involving a carbamate protected nitrogen and the first examples of any type of 5-*endo-trig* cyclisation onto a vinylsilane.

4. Experimental

4.1. General

All non-aqueous reactions were carried out under an oxygen-free atmosphere of nitrogen in flame-dried glassware with rigorous exclusion of moisture. All reactions were monitored by thin layer chromatography using Merck 5554 $60F_{254}$ silica gel coated plates. Visualisation was achieved using ultraviolet light and then either potassium permanganate or anisaldehyde. Flash-column chromatography was performed using Merck silica gel 60 as the stationary phase and Fisher, certified or specified grade solvents. Solvents and reagents were either used as supplied or, when necessary, purified in accordance with standard procedures as described below. Acetonitrile (bp 82 °C), DMPU (bp 146 °C at 44 mm Hg) and triethylamine (bp 89 °C) were distilled from calcium hydride and stored over 4 Å molecular sieves. Anhydrous grade dichloromethane (bp 39 °C) was distilled from calcium hydride immediately prior to use. Anhydrous grade tetrahydrofuran (bp 66 °C) was freshly distilled from sodium/benzophenone ketyl immediately prior to use. 18-crown-6 was recrystallised from acetonitrile. For work-up purposes, standard laboratory grade solvents were used as supplied.

*4.1.1. Allyl chlorides (**2**–**4**).* To a stirred solution of alcohol **1** (85 mg, 0.41 mmol) in Et_2O (2 mL) was added dropwise via cannula a solution of thionyl chloride (59 mg, 0.50 mmol) in Et_2O (1 mL+0.5 mL wash). The reaction was stirred for 20 h, after which time the crude material was adsorbed onto silica. Gel filtration (eluting with pet. ether) furnished chlorides **2**, **3** and **4** (91 mg, 98%) as an inseparable mixture in a ratio of 20:3:1; R_f=0.51 (100% pet. ether); IR ν_{max} (film)

3070–2914 (C–H), 1613, 1427, 1251, 1131, 1116, 1068 cm^{-1}; ^1H NMR **2** (400 MHz, $CDCl_3$) δ 0.52 (6H, s, Si(CH_3)$_2$), 1.68 (3H, d, J=7.1, C=CHCH_3), 4.22 (2H, s, CH_2Cl), 6.57 (1H, q, J=7.0, C=CHCH$_3$), 7.38–7.41 (3H, m, ArH), 7.56–7.62 (2H, m, ArH); ^1H NMR **4** (400 MHz, $CDCl_3$) δ 0.43 (3H, s, Si(CH_3)$_2$), 0.52 (3H, s, Si(CH_3)$_2$), 1.56 (3H, d, J=6.7, CHCH_3), 4.74 (1H, q, J=6.7, CHCH$_3$), 5.59 (1H, s, C=CH_2), 6.12 (1H, s, C=CH_2), 7.38–7.41 (3H, m, ArH), 7.56–7.62 (2H, m, ArH); ^1H NMR **3** (400 MHz, $CDCl_3$) δ 0.52 (6H, s, Si(CH_3)$_2$), 1.87 (3H, d, J=6.8, C=CHCH_3), 4.19 (2H, s, CH_2Cl), 6.19 (1H, q, J=6.7, C=CHCH$_3$), 7.38–7.41 (3H, m, ArH), 7.56–7.62 (2H, m, ArH); ^{13}C NMR **2** (400 MHz, $CDCl_3$) δ −1.7 (Si(CH_3)$_2$), 18.2 (C=CHCH_3), 52.3 (CH_2Cl), 127.9 (CH), 129.7 (CH), 134.1 (CH), 137.6 (C), 138.5 (C), 144.7 (CH). Anal. Calcd for $C_{12}H_{17}ClSi$: C 64.11, H 7.62, found: C 63.97, H 7.58 %.

*4.1.2. Glycine ester rearrangement precursor (**5a**).* Prepared according to the method previously reported for the allyl bromide, but with the addition of tetra-*n*-butyl ammonium iodide.[7d] Data was also identical to that reported earlier.[7d]

*4.1.3. Alanine, phenylalanine and valine ester rearrangement precursors (**5b**–**d**).* Prepared according to the method previously reported for the allyl bromide, but with the addition of tetra-*n*-butyl ammonium iodide.[12] Data was also identical to that reported earlier.[12]

4.1.4. (2S,3R*,4R*)-2-Diethylcarbamoyl-4-(dimethylphenylsilanyl)-2,3-dimethylpyrrolidine-1-carboxylic acid tert-butyl ester (**7**).* To a stirred suspension of KH (223 mg, 30% suspension in mineral oil, washed twice with pet. ether, 5.56 mmol) in THF (16 mL) at 0 °C was added **6** (801 mg, 1.85 mmol) and 18-crown-6 (490 mg, 1.85 mmol) in THF (5 mL+1 mL wash). The reaction was stirred for 1 h, then quenched with saturated aq NH_4Cl (10 mL). Et_2O (10 mL) was added and the layers were separated. The aqueous layer was re-extracted with Et_2O (10 mL) and the combined organic layers were washed with water (15 mL) then brine (15 mL), dried ($MgSO_4$) and concentrated in vacuo. Purification by flash-column chromatography (50% Et_2O/pet. ether) yielded **7** (602 mg, 75%) as a colourless oil; R_f=0.32 (50% Et_2O/pet. ether); IR ν_{max} (solution in $CHCl_3$) 2975 (C–H), 1681 (C=O), 1629 (C=O), 1455, 1374, 1114 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 0.26–0.47 (6H, m, Si(CH_3)$_2$), 0.88$_{rot.}$, 0.92$_{rot.}$ (3H, d, J=6.8, CHCH_3), 0.98–1.05 (6H, m, N(CH$_2$CH_3)$_2$), 1.32$_{rot.}$, 1.38$_{rot.}$ (9H, s, C(CH_3)$_3$), 1.50–1.53 (4H, m, CCH_3, CHSiMe$_2$Ph), 2.29$_{rot.}$, 2.38$_{rot.}$ (1H, br quintet, J=6.6, CHCH$_3$), 3.00–3.55 (6H, m, NCH_2, N(CH_2CH$_3$)$_2$), 7.37–7.40 (3H, m, ArH), 7.47–7.48 (2H, m, ArH); ^{13}C NMR (500 MHz, DMSO-d_6) δ −2.0 (Si(CH_3)$_2$), 13.3 (CH_3), 13.6 (CH_3), 21.1 (CH_3), 22.4 (CH_3), 27.3 (CH_3), 27.6 (CH_3), 28.5 (CH), 28.8 (CH), 42.9 (CH), 43.9 (CH), 48.1 (CH_2), 48.6 (CH_2), 71.5 (C), 71.7 (C), 78.3 (C), 78.6 (C), 128.4 (ArCH), 129.7 (ArCH), 133.7 (ArCH), 138.3 (ArC), 155.7 (C=O), 171.4 (C=O), 171.9 (C=O); ^{13}C NMR (270 MHz, DMSO-d_6, 80 °C) δ −2.8 (Si(CH_3)$_2$), −2.1 (Si(CH_3)$_2$), 13.5, 13.6, 21.5, 27.8, 28.8, 43.5, 48.6, 71.9, 78.7, 128.4, 129.6, 133.9, 138.5, 172.1 (C=O), two peaks missing; m/z (ES$^+$) 455 (100%, MNa$^+$), 333 (60%, MH$^+$); HRMS $C_{24}H_{40}N_2NaO_3Si$ calcd 455.2700, found 455.2681.

4.1.5. (2S,3R*,4R*)-4-(Dimethylphenylsilanyl)-2,3-dimethylpyrrolidine-2-carboxylic acid diethylamide (**9**).* To Boc-protected pyrrolidine **7** (200 mg, 0.463 mmol) was added, with stirring, HCl (3 equiv of 4 M solution in dioxane). The reaction was stirred for 3 h, after which time the solvent was removed in vacuo. The residue was taken up in CH_2Cl_2 (3 mL) and saturated aq $NaHCO_3$ (3 mL/mmol) added. The layers were separated and the aqueous layer was re-extracted with CH_2Cl_2 (5 mL/mmol). The combined organic layers were washed with brine (2×10 mL), dried ($MgSO_4$) and the solvent removed in vacuo to yield the crude pyrrolidine **9**, which was purified by column chromatography using SCX powder. Before loading the product, the column was flushed with AcOH (5% in MeOH), then MeOH. The crude material was loaded in CH_2Cl_2 and the column was once again flushed with MeOH. Methanolic ammonia (2%) was then used as the eluent to furnish **9** (132 mg, 86%) as a colourless oil; IR ν_{max} (solution in CH_2Cl_2) 3019 (N–H), 2873 (C–H), 1615 (C=O), 1360, 1215, 1109, 1064 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.27 (3H, s, Si(CH_3)$_2$), 0.35 (3H, s, Si(CH_3)$_2$), 0.93 (3H, d, J=7.2, CHCH_3), 1.11 (6H, t, J=7.0, N(CH$_2$CH_3)$_2$), 1.27 (3H, s, CCH_3), 1.46 (1H, ddd, J=11.8, 9.0, 5.9, CHSiMe$_2$Ph), 2.53 (1H, app. quintet, J=6.6, CHCH$_3$), 2.99 (1H, app. t, J=11.1, NCH_2), 3.13 (1H, app. t, J=9.6, NCH_2), 3.25–3.50 (4H, br m, N(CH_2CH$_3$)$_2$), 7.33–7.34 (3H, m, ArH), 7.48–7.49 (2H, m, ArH); ^{13}C NMR (500 MHz, $CDCl_3$) δ −3.0 (Si(CH_3)$_2$), −2.3 (Si(CH_3)$_2$), 12.6 (CH_3), 13.6 (CH_3), 13.9 (CH_3), 21.9 (CH_3), 32.3 (CH), 41.1 (CH_2), 41.3 (CH), 42.7 (CH_2), 45.7 (CH_2), 70.5 (C), 127.8 (ArCH), 129.0 (ArCH), 133.8 (ArCH), 138.8 (ArC), 176.3 (C=O); m/z (ES$^+$) 333 (100%, MH$^+$); HRMS $C_{19}H_{33}N_2OSi$ calcd 333.2357, found 333.2357.

4.1.6. (2R,3R*,4R*)-4-(Dimethylphenylsilanyl)-2,3-dimethylpyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester 2-methyl ester (**12b**).* To a stirred solution of **5b** (616 mg, 1.58 mmol), dried by azeotrope from toluene, in THF/DMPU (4:1, 5 mL) at 0 °C was added KMHDS (2.5 equiv of 0.5 M solution in toluene) dropwise. The reaction was stirred for 48 h, allowing to warm to rt. The reaction was then quenched with saturated aq NH_4Cl (5 mL) and Et_2O (5 mL) added. The layers were separated and the aqueous layer was re-extracted with Et_2O (2×5 mL). The combined organic layers were washed with brine (2×15 mL), dried ($MgSO_4$) and the solvent removed in vacuo. The crude products were purified by flash-column chromatography (25% Et_2O/pet. ether) to furnish **12b** (420 mg, 41%) as a colourless oil; R_f=0.22 (25% Et_2O/pet. ether); IR ν_{max} (solution in $CHCl_3$) 2954–2879 (C–H), 1732 (C=O), 1683 (C=O), 1392, 1368, 1118 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 0.30–0.35 (6H, m, Si(CH_3)$_2$), 0.89$_{rot.}$, 0.91$_{rot.}$ (3H, d, J=7.3, CHCH_3), 1.30–1.43 (12H, m, C(CH_3)$_3$, CCH_3), 1.77 (1H, ddd, J=12.5, 8.1, 6.2, CHSiMe$_2$Ph), 2.27$_{rot.}$, 2.36$_{rot.}$ (1H, app. quintet, J=6.7, CHCH$_3$), 3.29–3.41 (1H, m, NCH_2), 3.55–3.66 (4H, m, NCH_2, OCH_3), 7.38–7.41 (3H, m, ArH), 7.49–7.54 (2H, m, ArH); ^{13}C NMR (500 MHz, DMSO-d_6) δ −2.4 (Si(CH_3)$_2$), −2.2 (Si(CH_3)$_2$), 13.9 (CH_3), 14.1 (CH_3), 19.7 (CH_3), 20.7 (CH_3), 28.3 (CH), 28.5 (CH), 28.6 (CH), 44.7 (CH), 45.9 (CH), 48.5 (CH_2), 48.7 (CH_2), 52.6 (CH_3), 52.7 (CH_3), 69.1 (C), 69.5 (C), 79.1 (C), 79.3 (C), 128.4 (CH), 128.5 (CH), 129.7 (CH), 133.9 (CH), 134.1 (CH), 138.1 (C), 138.2 (C), 154.0 (C=O), 175.1 (C=O), 175.4 (C=O); ^{13}C NMR (270 MHz, DMSO-d_6, 80 °C) δ −2.6 (Si(CH_3)$_2$), −2.1 (Si(CH_3)$_2$), 14.0, 28.7, 28.9, 48.8, 52.5, 69.2, 79.1, 128.4, 129.7, 133.9, 138.4, 153.5 (C=O), three peaks missing; m/z (ES$^+$) 414 (100%, MNa$^+$), 358 (73%, MNa$^+$−C$_4$H$_8$), 314 (93%, MNa$^+$−Boc); HRMS $C_{21}H_{33}NNaO_4Si$ calcd 414.2071, found 414.2075. Compound **10b** (68 mg, 11%, dr 10) was also isolated and had identical data to that reported.[12]

4.1.7. (2R,3R*,4R*)-4-(Dimethylphenylsilanyl)-2,3-dimethylpyrrolidine-2-carboxylic acid methyl ester (**13b**).* Boc-protected proline **12b** (100 mg, 0.256 mmol) was deprotected according to the method for **9** except that **13b** (72 mg, 98%) was isolated as a colourless oil with no need for further purification. IR ν_{max} (solution in $CHCl_3$) 3168 (N–H), 2958 (C–H), 1710 (C=O), 1454, 1372, 1039 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 0.35 (3H, s, Si(CH_3)$_2$), 0.42 (3H, s, Si(CH_3)$_2$), 0.99 (3H, d, J=7.3, CHCH_3), 1.37 (3H, s, CCH_3), 1.80 (1H, ddd, J=11.2, 9.4, 6.4, CHSiMe$_2$Ph), 2.12 (1H, br s, NH), 2.81 (1H, app. quintet, J=7.0, CHCH$_3$), 3.18 (1H, app. t, J=10.5, NCH_2), 3.28 (1H, app. t, J=9.6, NCH_2), 3.39 (3H, s, OCH_3), 7.29–7.32 (3H, m, ArH), 7.51–7.52 (2H, m, ArH); ^{13}C NMR (400 MHz, $CDCl_3$) δ −0.7 (Si(CH_3)$_2$), 0.0 (Si(CH_3)$_2$), 16.1 (CH_3), 23.8 (CH_3), 34.3 (CH), 44.5 (CH), 48.6 (NCH_2), 73.0 (NHC), 130.3 (ArCH), 131.6 (ArCH), 136.2 (ArCH),

141.1 (ArC), 181.5 (C=O); *m/z* (ES^+) 292 (100%, MH^+); HRMS $C_{16}H_{26}NO_2Si$ calcd 292.1727, found 292.1730.

4.1.8. (2R,3R*,4R*)-2-Benzyl-4-(dimethylphenylsilanyl)-3-methylpyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester 2-methyl ester (**12c**).* Cyclisation of **5c** (103 mg, 0.221 mmol) was achieved via the conditions for **12b**, except stirring for 14 h. Purification by flash-column chromatography (25% Et_2O/pet. ether) gave **12c** (36 mg, 35%) as a colourless oil; R_f=0.19 (25% Et_2O/pet. ether); IR ν_{max} (solution in $CHCl_3$) 2978 (C–H), 1732, (C=O), 1683 (C=O), 1393, 1367, 1114 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.05–0.32 (6H, m, Si(CH_3)$_2$), 0.73–0.85 (3H, m, CHCH_3), 1.13$_{rot.}$, 1.42$_{rot.}$, 1.46$_{rot.}$ (9H, s, C(CH_3)$_3$), 1.82–1.98 (1H, m, C*H*SiMe$_2$Ph), 2.56$_{rot.}$, 2.71$_{rot.}$ (1H, app. quintet, *J*=8.4, C*H*CH$_3$), 2.97–3.85 (7H, m, NCH_2, OCH_3, CH_2Ph), 7.13–7.23 (5H, m, Ar*H*), 7.35–7.38 (3H, m, Ar*H*), 7.51–7.53 (2H, m, Ar*H*); ^{13}C NMR (500 MHz, DMSO-d_6) δ −2.6 (Si(CH_3)$_2$), −2.1 (Si(CH_3)$_2$), 16.0 (*C*H$_3$), 28.0 (*C*H), 28.6 (*C*H), 28.8 (*C*H), 29.1 (*C*H), 36.6 (*C*H$_2$), 37.2 (*C*H$_2$), 45.1 (*C*H), 47.3 (*C*H), 48.8 (*C*H$_2$), 52.6 (*C*H$_3$), 72.0 (*C*), 73.0 (*C*), 79.5 (*C*), 79.6 (*C*), 126.3 (*C*H), 127.2 (*C*H), 128.3 (*C*H), 128.4 (*C*H), 128.7 (*C*H), 129.7 (*C*H), 130.4 (*C*H), 130.6 (*C*H), 130.7 (*C*H), 133.6 (*C*H), 133.9 (*C*H), 134.0 (*C*H), 138.2 (*C*), 138.7 (*C*), 138.8 (*C*), 153.4 (*C*=O), 174.3 (*C*=O); ^{13}C NMR (270 MHz, DMSO-d_6, 80 °C) δ −2.5 (Si(CH_3)$_2$), −2.0 (Si(CH_3)$_2$), 15.8, 28.5, 29.3, 37.1, 46.2, 49.0, 52.2, 72.7, 79.6, 126.3, 128.3, 128.5, 129.7, 130.5, 130.8, 133.7, 134.0, 138.4, 138.9, 153.9 (*C*=O), 174.4 (*C*=O); *m/z* (ES^+) 490 (100%, MNa^+), 434 (74%, $MNa^+-C_4H_8$), 390 (61%, MNa^+–Boc); HRMS $C_{27}H_{37}NNaO_4Si$ calcd 490.2384, found 490.2407. Compound **10c** (38 mg, 37%) was also isolated and had identical data to that reported.[12]

4.1.9. (2R,3R*,4R*)-2-Benzyl-4-(dimethylphenylsilanyl)-3-methylpyrrolidine-2-carboxylic acid methyl ester (**13c**).* Boc protected proline **12c** (48 mg, 0.10 mmol) was deprotected according to the method for **9** except that **13b** (37 mg, 98%) was isolated as a colourless oil with no need for further purification. IR ν_{max} (solution in $CHCl_3$) 3341 (N–H), 2952–2873 (C–H), 1727 (C=O), 1455, 1375, 1110, 1049 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.38 (3H, s, Si(CH_3)$_2$), 0.44 (3H, s, Si(CH_3)$_2$), 1.16 (3H, d, *J*=7.2, CHCH_3), 1.55 (1H, ddd, *J*=11.2, 9.9, 6.2, C*H*SiMe$_2$Ph), 2.45 (1H, br s, N*H*), 2.77 (1H, app. quintet, *J*=6.7, C*H*CH$_3$), 2.84 (1H, d, *J*=12.8, CH_2Ph), 3.12 (1H, d, *J*=12.8, CH_2Ph), 3.20 (1H, dd, *J*=11.2, 10.2, NCH_2), 3.27 (1H, app. t, *J*=9.8, NCH_2), 3.63 (3H, s, OCH_3), 7.19–7.20 (2H, m, Ar*H*), 7.24–7.32 (3H, m, Ar*H*), 7.41–7.44 (3H, m, Ar*H*), 7.54–7.57 (2H, m, Ar*H*); ^{13}C NMR (500 MHz, $CDCl_3$) δ −3.0 (Si(CH_3)$_2$), −2.6 (Si(CH_3)$_2$), 14.0 (CHCH_3), 31.3 (C*H*SiMe$_2$Ph), 41.8 (CH_2Ph), 43.1 (C*H*CH$_3$), 45.8 (NCH_2), 52.1 (OCH_3), 75.6 (NH*C*), 126.6 (Ar*C*H), 127.9 (Ar*C*H), 128.3 (Ar*C*H), 129.1 (Ar*C*H), 129.5 (Ar*C*H), 133.8 (Ar*C*H), 138.0 (Ar*C*), 138.7 (Ar*C*), 177.5 (*C*=O); *m/z* (ES^+) 390 (94%, MNa^+), 368 (47%, MH^+), 308 (48%); HRMS $C_{22}H_{29}NNaO_2Si$ calcd 390.1860, found 390.1845.

4.1.10. (2R,3R*,4R*)-4-(Dimethylphenylsilanyl)-2-isopropyl-3-methyl-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester 2-methyl ester (**12d**).* Cyclisation of **5d** (1.68 g, 4.01 mmol) was achieved via the conditions for **12b** and after purification by column chromatography (20% Et_2O/pet. ether) gave **12d** (1.34 g, 87%) as a colourless solid (mp 72.1–73.3 °C); R_f=0.21 (20% Et_2O/pet. ether); IR ν_{max} (solution in $CHCl_3$) 2967–2878 (C–H), 1733 (C=O), 1682 (C=O), 1392, 1367, 1350, 1113 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 0.30$_{rot.}$, 0.32$_{rot.}$, 0.37$_{rot.}$ (6H, s, Si(CH_3)$_2$), 0.79 (3H, d, *J*=7.3, CH(CH_3)$_2$), 0.82$_{rot.}$, 0.84$_{rot.}$ (3H, d, *J*=6.8, CH(CH_3)$_2$), 1.12 (3H, app. t, *J*=6.7, CHCH_3), 1.37$_{rot.}$, 1.46$_{rot.}$ (9H, s, C(CH_3)$_3$), 1.70–1.84 (1H, m, C*H*SiMe$_2$Ph), 2.63 (1H, app. sextet, *J*=6.7, C*H*(CH$_3$)$_2$), 2.74 (1H, app. septet, *J*=6.9, C*H*CH$_3$), 3.34–3.58 (5H, m, NCH_2, OCH_3), 7.38–7.40 (3H, m, Ar*H*), 7.52–7.54 (2H, m, Ar*H*); ^{13}C NMR (270 MHz, DMSO-d_6) δ −2.3 (Si(CH_3)$_2$), −2.1 (Si(CH_3)$_2$), −1.8 (Si(CH_3)$_2$), 17.4 (*C*H$_3$), 17.5 (*C*H$_3$), 19.8 (*C*H$_3$), 20.3 (*C*H$_3$), 28.3 (*C*H$_3$), 28.5 (*C*H$_3$), 30.5 (*C*H), 31.4 (*C*H), 31.9 (*C*H), 32.9 (*C*H), 38.8 (*C*H), 49.9 (*C*H$_2$), 50.1 (*C*H$_2$), 51.3 (*C*H$_3$), 51.5 (*C*H$_3$), 75.9 (*C*), 76.4 (*C*), 79.2 (*C*), 79.3 (*C*), 128.4 (Ar*C*H), 129.6 (Ar*C*H), 133.9 (Ar*C*H), 138.4 (Ar*C*), 153.5 (*C*=O), 154.1 (*C*=O), 173.7 (*C*=O), 174.0 (*C*=O); ^{13}C NMR (270 MHz, DMSO-d_6, 80 °C) δ −2.4 (Si(CH_3)$_2$), −1.8 (Si(CH_3)$_2$), 17.4, 19.8, 20.0, 28.6, 30.8, 32.6, 50.3, 51.2, 76.6, 79.4, 128.5, 129.6, 133.9, 138.7, 153.7 (*C*=O), 173.7 (*C*=O); *m/z* (ES^+) 442 (40%, MNa^+), 320 (100%, MH^+–Boc); HRMS $C_{23}H_{37}NNaO_4Si$: calcd 422.2384, found 442.2387; Anal. Calcd for $C_{23}H_{37}NO_4Si$: C 65.83, H 8.89, N 3.34, found C 65.57, H 8.90, N 3.29%. Suitable crystals for X-ray analysis were grown from Et_2O/Petrol.

4.1.11. (2R,3R*,4R*)-4-(Dimethyphenylsilanyl)-2-isopropyl-2-methoxy-carbonyl-3-methylpyrrolidium chloride (**13d**).* Boc protected proline **12d** (156 mg, 0.372 mmol) was deprotected according to the method for **9** except that **13d** (131 mg, 99%) was isolated as a colourless solid (mp 80.4–81.5 °C) with no need for further purification. IR ν_{max} (solution in $CHCl_3$) 2926–2854 (C–H), 1746 (C=O), 1459, 1380, 1266, 1113 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.38 (3H, s, Si(CH_3)$_2$), 0.44 (3H, s, Si(CH_3)$_2$), 0.96 (3H, d, *J*=7.3, CHCH_3), 1.12 (3H, d, *J*=6.9, CH(CH_3)$_2$), 1.21 (3H, d, *J*=6.8, CH(CH_3)$_2$), 1.99 (1H, ddd, *J*=13.7, 8.4, 6.4, C*H*SiMe$_2$Ph), 2.32 (1H, septet, *J*=6.8, C*H*(CH$_3$)$_2$), 2.69 (1H, app. quintet, *J*=6.8, C*H*CH$_3$), 3.73 (1H, app. t, *J*=12.5, NCH_2), 3.79 (3H, s, OCH_3), 3.88 (1H, dd, *J*=11.4, 8.5, NCH_2), 7.36–7.40 (3H, m, Ar*H*), 7.49–7.51 (2H, m, Ar*H*), 9.55 (1H, br s, N*H*); ^{13}C NMR (270 MHz, DMSO-d_6) δ −3.1 (Si(CH_3)$_2$), −2.3 (Si(CH_3)$_2$), 15.2 (CHCH_3), 17.8 (CH(CH_3)$_2$), 18.4 (CH(CH_3)$_2$), 29.8 (C*H*SiMe$_2$Ph), 32.8 (C*H*(CH$_3$)$_2$), 41.6 (C*H*CH$_3$), 47.1 (NCH_2), 52.7 (OCH_3), 81.6 (N*C*), 128.4 (Ar*C*H), 129.8 (Ar*C*H), 133.6 (Ar*C*H), 136.6 (Ar*C*), 169.2 (*C*=O); *m/z* (ES^+) 320 (100%, MH^+–HCl); HRMS $C_{18}H_{30}NO_2Si$: calcd 320.2046, found 320.2036.

*4.1.12. Terminal alkene rearrangement precursor (**16**).* To a stirred suspension of KH (44 mg, 1.1 mmol) in THF (3 mL) at 0 °C was added a solution of Boc-(*L*)-valine methyl ester (231 mg, 1.00 mmol) in THF (3 mL). The reaction was stirred for 1 h at 0 °C, then 1-bromo-2-(phenyldimethylsilyl)-prop-2-ene[7d] (306 mg, 1.20 mmol) in THF (2 mL) was added. The reaction was stirred for a further 14 h, then quenched with saturated aq NH_4Cl (5 mL). Et_2O (4 mL) was added and the layers separated. The aqueous layer was re-extracted with Et_2O (5 mL) and the combined organic layers were washed with water (10 mL), brine (10 mL), dried ($MgSO_4$) and concentrated in vacuo. Purification by flash-column chromatography (25% Et_2O/pet. ether) yielded **16** (320 mg, 79%) as a colourless oil; R_f=0.37 (25% Et_2O/pet. ether); $[\alpha]_D^{20}$ −26.5 (*c*, 2.1, $CHCl_3$); IR ν_{max} (solution in $CHCl_3$) 2965–2876 (C–H), 1737 (C=O), 1683 (C=O), 1455, 1391, 1368, 1329, 1138, 1110 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.39 (3H, s, Si(CH_3)$_2$), 0.40 (3H, s, Si(CH_3)$_2$), 0.86 (3H, d, *J*=6.8, CH(CH_3)$_2$), 0.90 (3H, d, *J*=6.5, CH(CH_3)$_2$), 1.40–1.48 (9H, m, C(CH_3)$_3$), 2.08–2.22 (1H, br m, C*H*(CH$_3$)$_2$), 3.59 (3H, s, OCH_3), 3.71–4.04 (3H, m, NCH_2, NC*H*), 5.35–5.42 (1H, br m, C=CH_2), 5.55–5.65 (1H, br m, C=CH_2), 7.34–7.37 (3H, m, Ar*H*), 7.52–7.54 (2H, m, Ar*H*); ^{13}C NMR (270 MHz, DMSO-d_6) δ −3.1 (Si(CH_3)$_2$), 18.4, 18.9, 19.5, 20.3, 28.0, 47.2 (*C*H$_2$), 49.0 (*C*H$_2$), 51.8 (*C*H), 62.9, 64.4, 79.4, 79.7, 121.8 (*C*H$_2$), 124.8 (*C*H$_2$), 128.0 (*C*H), 129.1 (*C*H), 133.5 (*C*H), 137.1 (*C*), 145.3 (*C*), 155.4 (*C*=O), 170.6 (*C*=O); ^{13}C NMR (270 MHz, DMSO-d_6, 80 °C) δ −3.9 (Si(CH_3)$_2$), −3.8 (Si(CH_3)$_2$), 18.1, 19.1, 27.4, 47.8, 50.7, 63.3, 78.8, 122.7, 127.2, 128.6, 133.1, 136.7, 144.7, 154.5 (*C*=O), 170.0 (*C*=O); *m/z* (ES^+) 428 (100%, MNa^+), 372 (27%, $MNa^+-C_4H_8$), 306 (16%, MH^+–Boc); HRMS $C_{22}H_{35}NNaO_4Si$ calcd 428.2228, found 428.2222; Anal. Calcd for $C_{22}H_{35}NO_4Si$: C 65.15, H 8.70, N 3.45, found C 65.12, H 8.78, N 3.21%.

*4.1.13. Rearrangement of **16** to give (2R,S)-2-tert-Butoxycarbonylamino-4-(dimethylphenylsilanyl)-2-isopropylpent-4-enoic acid methyl ester (**17**) and (2S*,4R*)-4-(dimethylphenylsilanyl)-2-isopropylpyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester 2-methyl*

*ester (**18**).* Treatment of **16** under the cyclisation conditions for **12b** gave a crude product that was purified by column chromatography (20% Et_2O/pet. ether) to yield **17** (36 mg, 14%) as a colourless oil and **18** (170 mg, 67%) as a colourless oil. Data for **17** R_f=0.45 (25% Et_2O/pet. ether); IR ν_{max} (solution in $CHCl_3$) 3421 (N–H), 2954 (C–H), 1715 (C=O), 1456, 1391, 1367, 1110, 1069 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.35 (3H, s, Si(CH_3)$_3$), 0.38 (3H, s, Si(CH_3)$_3$), 0.84 (3H, d, J=6.9, CH(CH_3)$_2$), 0.88 (3H, d, J=6.9, CH(CH_3)$_2$), 1.43 (9H, s, C(CH_3)$_3$), 2.44 (1H, septet, J=6.9, CH(CH_3)$_2$), 2.74 (1H, d, J=16.1, CH_2), 3.40 (1H, d, J=16.1, CH_2), 3.58 (3H, s, OCH_3), 5.47 (1H, s, C=CH_2 or NH), 5.55 (1H, s, C=CH_2 or NH), 5.75 (1H, s, C=CH_2 or NH), 7.35–7.36 (3H, m, ArH), 7.50–7.52 (2H, m, ArH); ^{13}C NMR (500 MHz, $CDCl_3$) δ −2.9 (Si(CH_3)$_2$), −2.4 (Si(CH_3)$_2$), 17.7 (CH(CH_3)$_2$), 17.8 (CH(CH_3)$_2$), 28.5 (C(CH_3)$_3$), 34.8 (CH(CH_3)$_2$), 36.3 (CH_2), 52.1 (OCH_3), 66.3 (C), 78.9 (C), 127.7 (ArCH), 128.2 (H_2C=C), 128.9 (ArCH), 134.1 (ArCH), 138.4 (C), 146.0 (C), 153.8 (C=O), 173.5 (C=O); m/z (ES^+) 428 (68%, MNa^+), 372 (92%, MNa^+−C_4H_8), 328 (100%, MNa^+−Boc); HRMS $C_{22}H_{35}NNaO_4Si$ calcd 428.2228, found 428.2222. Data for **18** R_f=0.28 (25% Et_2O/pet. ether); IR ν_{max} (solution in $CHCl_3$) 2968 (C–H), 1710 (C=O), 1494, 1392, 1367, 1110 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.30 (6H, s, Si(CH_3)$_2$), 0.90 (3H, d, J=6.3, CH(CH_3)$_2$), 1.11 (3H, d, J=6.6, CH(CH_3)$_2$), 1.40$_{rot.}$, 1.43$_{rot.}$ (9H, s, C(CH_3)$_3$), 1.57–1.65 (1H, m, CHSiMe$_2$Ph), 1.92 (1H, app. t, J=13.3, CCH_2), 2.19$_{rot.}$, 2.26$_{rot.}$ (1H, dd, J=12.8, 7.8, CCH_2), 2.68$_{rot.}$, 2.78$_{rot.}$ (1H, septet, J=6.8CH(CH_3)$_2$), 3.35$_{rot.}$, 3.45$_{rot.}$ (1H, app. t, J=11.7, NCH_2), 3.60 (3H, s, OCH_3), 3.67$_{rot.}$, 3.75$_{rot.}$ (1H, app t, J=9.5, NCH_2), 7.36–7.37 (3H, m, ArH), 7.49–7.50 (2H, m, ArH); ^{13}C NMR (500 MHz, $CDCl_3$) δ −5.0 (Si(CH_3)$_2$), −1.7 (Si(CH_3)$_2$), 19.2 (CH_3), 19.6 (CH_3), 24.0 (CH), 24.9 (CH), 28.1 (CH_3), 28.3 (CH_3), 30.9 (CH), 31.4 (CH), 34.2 (CH_2), 35.2 (CH_2), 51.1 (CH_2), 51.4 (CH_2), 51.5 (CH_3), 52.1 (CH_3), 71.5 (C), 72.0 (C), 79.3 (C), 80.0 (C), 127.8 (ArCH), 129.2 (ArCH), 133.6 (ArCH), 136.7 (ArC), 153.9 (C=O), 175.0 (C=O); m/z (ES^+) 428 (100%, MNa^+); HRMS $C_{22}H_{35}NNaO_4Si$ calcd 428.2228, found 428.2225.

4.1.14. (2S,4R*)-4-(Dimethylphenylsilanyl)-2-isopropylpyrrolidine-1,2-dicarboxylic acid 2-methyl ester (**19**).* Boc protected proline **18** (99 mg, 0.24 mmol) was deprotected according to the method for **9** except that **19** (73 mg, 96%) was isolated as a colourless oil with no need for further purification. IR ν_{max} (solution in CH_2Cl_2) 3020 (N–H), 2925 (C–H), 1722 (C=O), 1216, 845 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.30 (6H, s, Si(CH_3)$_2$), 0.87 (3H, d, J=6.7, CH(CH_3)$_2$), 0.94 (3H, d, J=6.8, CH(CH_3)$_2$), 1.52–1.69 (2H, m, CHSiMe$_2$Ph, NH), 1.90–2.03 (3H, m, CCH_2, CH(CH_3)$_2$), 2.69 (1H, dd, J=12.5, 9.3, NCH_2), 3.07 (1H, dd, J=9.2, 6.9, NCH_2), 3.71 (3H, s, OCH_3), 7.32–7.42 (3H, m, ArH), 7.53–7.54 (2H, m, ArH); ^{13}C NMR (500 MHz, $CDCl_3$) δ −2.8 ((SiCH_3)$_2$), −2.5 (Si(CH_3)$_2$), 18.0 (CH_3), 25.7 (CH), 31.2 (CH), 35.5 (CH_2), 53.2 (CH_2), 62.1 (CH_3), 71.4 (C), 127.7 (ArCH), 128.7 (ArCH), 133.9 (ArCH), 138.2 (ArC), 173.9 (C=O); m/z (ES^+) 306 (100%, MH^+); HRMS $C_{17}H_{28}NO_2Si$ calcd 306.1884, found 306.1885.

4.1.15. (2R,3R*,4R*)-4-Hydroxy-2-isopropyl-3-methylpyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester 2-methyl ester (**20**).* To a stirred solution of **12d** (52 mg, 0.12 mmol) in peracetic acid solution (0.13 mL of 36–40 wt % solution in AcOH, 0.62 mmol) was added mercury (II) acetate (47 mg, 0.15 mmol). The reaction was stirred for 4 h then Et_2O (1 mL) was added. The solution was washed with saturated aq sodium thiosulfate (1 mL), water (1 mL), saturated aq $NaHCO_3$ (1 mL) and brine (1 mL). The organic layer was then dried ($MgSO_4$) and concentrated in vacuo. The crude product was purified by flash-column chromatography (40% Et_2O/pet. ether) to yield **20** (25 mg, 67%) as a colourless oil; R_f=0.38 (40% Et_2O/pet. ether); IR ν_{max} (solution in CH_2Cl_2) 3445 (O–H), 2876 (C–H), 1752 (C=O), 1690 (C=O), 1398, 1368, 1139, 1110, 1076 cm^{-1}; ^1H NMR (270 MHz, DMSO-d_6) δ 0.73$_{rot.}$, 0.74$_{rot.}$ (3H, d, J=7.0, CH(CH_3)$_2$), 0.91 (3H, d, J=7.2, CHCH_3), 1.09$_{rot.}$, 1.10$_{rot.}$ (3H, d, J=7.0, CH(CH_3)$_2$), 1.33$_{rot.}$, 1.39$_{rot.}$ (9H, s, C(CH_3)$_3$), 2.35–2.47 (1H, m, CHCH$_3$), 2.72$_{rot.}$, 2.79$_{rot.}$ (1H, septet, J=6.9, CH(CH_3)$_2$), 3.22$_{rot.}$, 3.30$_{rot.}$ (1H, dd, J=11.8, 4.0, NCH_2), 3.55–3.65 (4H, m, OCH_3, NCH_2), 3.95 (1H, app. dt, J=8.4, 4.5, CHOH), 4.23$_{rot.}$, 4.27$_{rot.}$ (1H, d, J=7.9, CHOH); ^{13}C NMR (400 MHz, C_6D_6) δ 11.8 (CH_3), 11.9 (CH_3), 16.9 (CH_3), 17.2 (CH_3), 18.9 (CH_3), 19.0 (CH_3), 28.3 (CH_3), 28.4 (CH_3), 30.8 (CH), 32.6 (CH), 41.1 (CH), 42.3 (CH), 51.5 (CH_3), 52.1 (CH_3), 57.1 (CH_2), 57.7 (CH_2), 72.8 (C), 72.9 (CH), 73.4 (C), 73.7 (CH), 79.6 (C), 79.7 (C), 153.1 (C=O), 154.1 (C=O), 174.5 (C=O), 175.5 (C=O); m/z (ES^+) 324 (100%, MNa^+); HRMS $C_{15}H_{27}NNaO_5$ calcd 324.1781, found 324.1773.

4.1.16. (2R,3S*)-2-Isopropyl-3-methylpyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester 2-methyl ester (**21**).* To a stirred solution of **12d** (26 mg, 62 μmol) in DMF (0.5 mL) was added TBAF (0.31 mL of 1 M solution in THF, 0.31 mmol). The reaction was heated to 80 °C and stirred for 2 h. The reaction was then allowed to cool to rt and diluted with EtOAc (1 mL) and pet. ether (1 mL). The solution was washed sequentially with 1 M aq HCl (1 mL), saturated aq $KHCO_3$ (1 mL) and brine (1 mL). The organic layer was then dried ($MgSO_4$) and concentrated in vacuo. Purification by flash-column chromatography (50% Et_2O/pet. ether) gave **21** (13 mg, 74%) as a colourless oil; R_f=0.44 (50% Et_2O/pet. ether); IR ν_{max} (solution in CH_2Cl_2) 2876 (C–H), 1740 (C=O), 1686 (C=O), 1398, 1367, 1216, 1118 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.79$_{rot.}$, 0.81$_{rot.}$ (3H, d, J=6.8, CH(CH_3)$_2$), 0.98$_{rot.}$, 0.99$_{rot.}$ (3H, d, J=6.5, CHCH_3), 1.14 (3H, d, J=7.0, CH(CH_3)$_2$), 1.39$_{rot.}$, 1.42$_{rot.}$ (9H, s, C(CH_3)$_3$), 1.65–1.86 (2H, m, NCH$_2$$CH_2$), 2.30–2.41 (1H, m, CHCH$_3$), 2.81$_{rot.}$, 2.95$_{rot.}$ (1H, septet, J=6.9, CH(CH_3)$_2$), 3.08 (1H, ddd, J=11.9, 10.8, 5.8, NCH_2), 3.66 (3H, s, OCH_3), 3.73$_{rot.}$, 3.85$_{rot.}$ (1H, app. dd, J=10.8, 8.3, NCH_2); ^{13}C NMR (270 MHz, DMSO-d_6) δ 17.0 (CH_3), 17.1 (CH_3), 17.2 (CH_3), 17.4 (CH_3), 18.9 (CH_3), 19.1 (CH_3), 28.3 (CH_3), 28.5 (CH_3), 31.0 (CH), 32.1 (CH_2), 32.3 (CH_2), 32.7 (CH_2), 37.1 (CH), 38.2 (CH), 47.5 (CH_2), 51.3 (CH_3), 72.6 (C), 72.8 (C), 79.3 (C), 79.9 (C), 153.4 (C=O), 153.6 (C=O), 173.5 (C=O), 173.6 (C=O); ^{13}C NMR (270 MHz, DMSO-d_6, 80 °C) δ 17.3, 17.5, 19.3, 28.6, 32.2, 32.4, 37.0, 38.0, 47.5, 51.4, 73.0, 79.3, 152.8 (C=O), 173.3 (C=O); m/z (ES^+) 308 (100%, MNa^+); HRMS $C_{15}H_{27}NNaO_4$ calcd 308.1832, found 308.1833.

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