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Ether-directed palladium(II)-catalysed aza-Claisen rearrangements: studies on the origin of the directing effect

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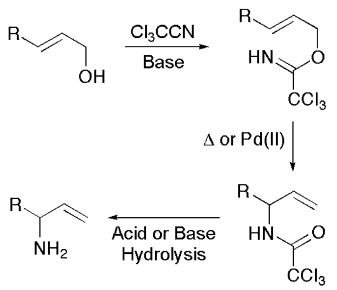
Abstract—Four new chiral δ-substituted allylic trichloroacetimidates have been synthesised to probe the origin of the high diastereoselectivity observed for the MOM-ether directed palladium(II)-catalysed aza-Claisen rearrangement. Rearrangement of these compounds has not only provided strong evidence for this directing effect but also that during the rearrangement both oxygen atoms from the MOM-ether are involved in coordinating to and directing the palladium(II) catalyst.

1. Introduction

The aza-Claisen rearrangement of allylic trichloroacetimidates, commonly known as the Overman rearrangement, involves the allylic interchange of alcohol and amino functional groups (Scheme 1).[1] This transformation has found widespread application in the synthesis of nitrogen containing organic molecules[2] mainly due to the excellent transfer of chirality to the final product via a highly ordered chair-like transition state.[3] As well as the thermal version of this reaction, which produces the allylic amide via a concerted suprafacial pathway, the metal-catalysed process is also well characterised allowing the reaction to proceed under mild conditions.[4–6] In fact, understanding of the metal-catalysed cyclisation-induced mechanism has led to the development of a number of chiral palladium(II) catalysts for the stereoselective synthesis of allylic amides.[7]



Scheme 1. Synthesis of allylic amines using the Overman rearrangement.

Keywords: Palladium catalysis; Aza-Claisen rearrangement; Directing effect.
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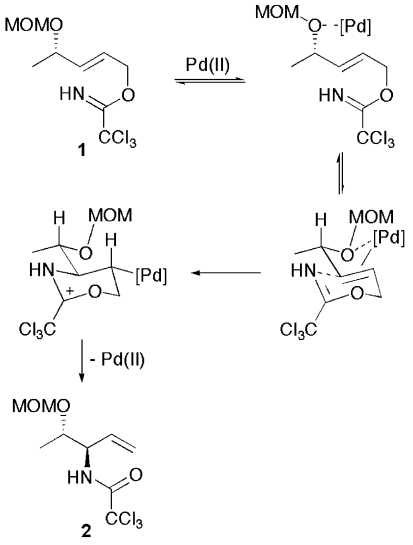
In an effort to understand how the rearrangement of chiral allylic trichloroacetimidates is influenced by stereogenic centres within the molecule, we initiated a programme to synthesise and test suitable substrates. This led to the development of a MOM-ether directed, palladium(II)-catalysed process, which produces the major *anti*-diastereomer in ratios of up to 15:1 (Scheme 2).[8] Evidence for this ether directing effect was obtained by the synthesis of a carbon analogue of the MOM-ether substrate **1** where both of the side-chain oxygen atoms were replaced by a methylene unit. Palladium(II)-catalysed rearrangement of this carbon analogue produced the corresponding allylic trichloroacetamide diastereomers in only a 2:1 ratio.[8a] More recently, further evidence has been attained by a solvent study, which showed that coordinating solvents compete with the MOM-ether for binding of the palladium(II) catalyst resulting in a suppression of the diastereoselective outcome, while non-coordinating solvents such as toluene lead to an enhancement of diastereoselectivity.[8b] With a substantial body of evidence for the ether directing effect during these rearrangements, we were surprised by a report from the group of Ham and co-workers whose results are in direct contrast to our own and seem to show that rearrangement of chiral δ-ether substituted allylic trichloroacetimidates are influenced by steric bulk and not by chelation between the ether oxygen and the palladium(II) catalyst.[9] While this study was carried out on slightly different compounds and using a different approach for analysis of diastereoselectivity to our own, the finding of this paper has prompted us to report our recent study on the origin of diastereoselectivity for these aza-Claisen rearrangements. Thus, we now report the synthesis and rearrangement of a new δ-hydroxy substituted allylic trichloroacetimidate as well as structural analogues of the original MOM-substrate, which not only show that a

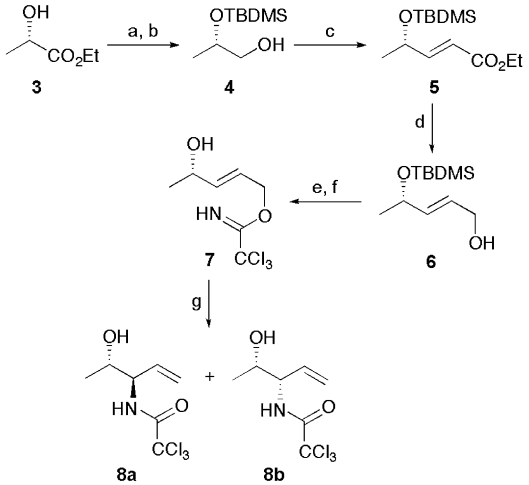
directing effect is responsible for the highly diastereoselective rearrangement but that both oxygen atoms of the MOM-ether are involved in coordinating to the palladium(II) catalyst.



Scheme 2. MOM-ether directed Pd(II)-catalysed rearrangement via the cyclisation-induced pathway.

2. Results and discussion

As well as utilising the ether-directed rearrangement for the highly diastereoselective synthesis of β- and γ-hydroxy-α-amino acids,[10] we have also been investigating the effect of other functional groups. Thus, our initial aim in this study was the synthesis of δ-hydroxyl substituted allylic trichloroacetimidate **7**, as it was proposed that the free hydroxyl group might bind more strongly to the catalyst than an ether oxygen atom resulting in a more selective rearrangement. Allylic trichloroacetimidate **7** was prepared in six steps as shown in Scheme 3. The hydroxyl group of ethyl (*S*)-lactate



Scheme 3. Reagents and conditions: (a) TBDMSCl, imidazole, THF, 100%; (b) DIBAL-H (2.2 equiv), Et_2O, −78 °C–rt, 61%; (c) DMSO, $(COCl)_2$, NEt_3, CH_2Cl_2, −78 °C–rt, then triethyl phosphonoacetate, LiCl, DBU, MeCN, 81%; (d) DIBAL-H (2.2 equiv), Et_2O, −78 °C–rt, 72%; (e) DBU, Cl_3CCN, CH_2Cl_2; (f) TBAF, THF; (g) $PdCl_2(MeCN)_2$, THF, 33% from **6**.

3 was protected as the *tert*-butyldimethylsilyl ether and this was reduced to primary alcohol **4** using DIBAL-H. A one pot Swern oxidation/Horner–Wadsworth–Emmons (HWE) reaction gave (*E*)-α,β-unsaturated ester **5** in 81% yield.[11] Masamune–Roush conditions are used for all of our HWE reactions mainly due to the mild conditions employed during this procedure.[12] Reduction of the ester functional group with 2.2 equiv of DIBAL-H then gave allylic alcohol **6**. This was then converted to the desired substrate **7** by formation of the allylic trichloroacetimidate using trichloroacetonitrile and DBU followed by deprotection of the silyl ether using TBAF. Allylic trichloroacetimidates prepared in this way are normally purified by washing quickly through a small plug of silica gel.[8,9] However, allylic trichloroacetimidate **7** is particularly unstable due to the free hydroxyl group and thus was used without purification.

Rearrangement of **7** using bis(acetonitrile)palladium(II) chloride in THF gave the corresponding allylic trichloroacetamides **8** in 33% yield from allylic alcohol **6** (over three steps) and surprisingly in only a 4:1 ratio in favour of the *anti*-diastereomer **8a**. The corresponding MOM-ether **1** rearranges under the same conditions in a 10:1 ratio and thus, the results for the hydroxyl derivative **7** represents a substantial drop in selectivity.[8a] The fact that the free hydroxyl group is unable to direct the catalyst as effectively as the MOM-group led to the proposal that both oxygen atoms of the MOM-group are involved in coordinating the palladium(II) catalyst resulting in the highly selective directed rearrangement. To probe this it was decided to synthesise two analogues of **1**, allylic trichloroacetimidates **9** and **10** (Fig. 1). Both of these compounds like the carbon analogue[8a] are approximately of the same size as **1** and thus if steric bulk is responsible for the diastereoselective outcome of these rearrangements as proposed by Ham and co-workers,[9] then the results should be similar for all of these compounds. However, if the selectivity of these rearrangements is controlled by the directing effect of the oxygen atoms then the results should be very different. More importantly, the synthesis and rearrangement of **9** and **10** would effectively demonstrate the ability of either oxygen atom to coordinate to the palladium(II) catalyst and whether both are required for the observed highly diastereoselective rearrangement of substrate **1**.

Allylic trichloroacetimidate **9** was prepared in six steps from ethyl (*S*)-lactate **3** (Scheme 4). The hydroxyl group of **3** was alkylated with allyl bromide and sodium hydride in quantitative yield. Hydrogenation of the allyl group under standard conditions then gave the required propyl derivative **11** in 71% yield.[13] The propyl protected lactate was then converted to allylic alcohol **14** using our standard approach for the synthesis of these compounds via the (*E*)-α,β-unsaturated ester **13**. Finally, treatment of **14** with DBU and trichloroacetonitrile gave allylic trichloroacetimidate **9**.

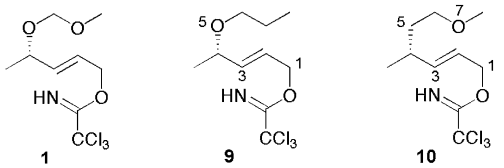
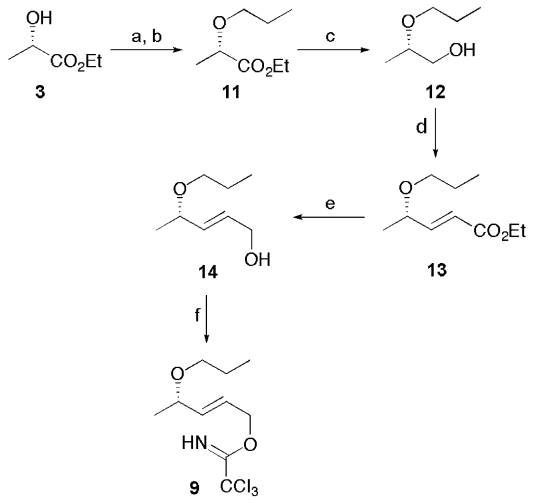


Figure 1.

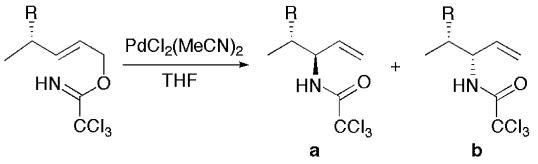


Scheme 4. Reagents and conditions: (a) NaH, allyl bromide, 100%; (b) H_2, 10% Pd/C, EtOH, 71%; (c) DIBAL-H (2.2 equiv), Et_2O, −78 °C–rt, 51%; (d) DMSO, $(COCl)_2$, NEt_3, CH_2Cl_2, −78 °C–rt, then triethyl phosphonoacetate, LiCl, DBU, MeCN, 41%; (e) DIBAL-H (2.2 equiv), Et_2O, −78 °C–rt, 66%; (f) DBU, Cl_3CCN, CH_2Cl_2.

For the synthesis of allylic trichloroacetimidate **10**, the Myers' approach of using pseudoephedrine as a chiral auxiliary was employed to introduce the stereogenic centre (Scheme 5).[14] Initially, γ-butyrolactone **15** was ring opened with sodium and methanol to give 4-methoxybutanoic acid **16**. The carboxylic acid was then activated as the mixed anhydride and coupled with (1*R*,2*R*)-(−)-pseudoephedrine **17**. The resulting amide **18** was alkylated with methyl iodide producing the major 2*R*-isomer in 65% yield. The pseudoephedrine auxiliary was then cleaved with lithium triethoxyaluminium hydride to give aldehyde **20** and this was treated in situ with triethyl phosphonoacetate under standard Masamune–Roush conditions to yield (*E*)-α,β-unsaturated ester **21**.[12] Reduction of the ester with DIBAL-H gave alcohol **22** and this was converted to allylic trichloroacetimidate **10** again using DBU and trichloroacetonitrile.

With both MOM-analogues in hand, these were then treated with bis(acetonitrile)palladium(II) chloride at room temperature (Table 1). Although we have recently shown that toluene gives the best diastereoselective outcome for this directed rearrangement,[8b] THF was used as the solvent for this study so that direct comparison with the original

Table 1. Pd(II)-catalysed rearrangement of the MOM-analogues

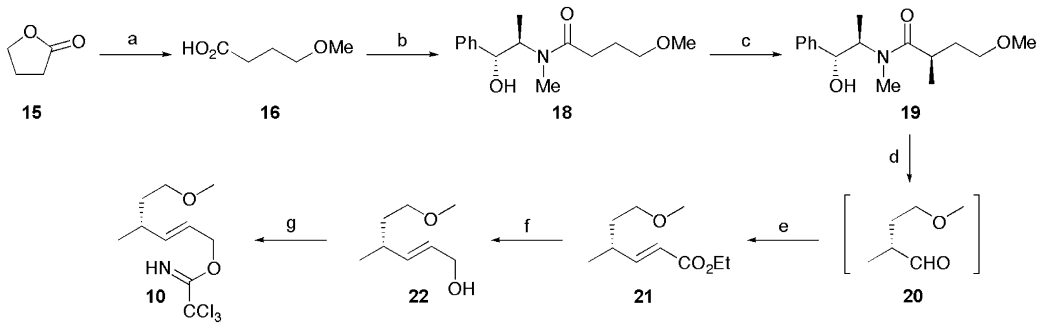


Entry	R	Yield[a] (%)	Ratio[b] (**a**:**b**)
1	OCH_2OCH_3 (**23**)	64	10:1
2	$CH_2CH_2CH_2CH_3$ (**24**)	59	1:2
3	$OCH_2CH_2CH_3$ (**25**)	77	5:1
4	$CH_2CH_2OCH_3$ (**26**)	60	1:2

[a] Isolated combined yields of **a** and **b** from *E*-allylic alcohol.
[b] Ratio in crude reaction mixture.

MOM-substrate **1** could be carried out.[8a] As previously reported,[8a] rearrangement of the MOM-derived allylic trichloroacetimidate **1** proceeds in high diastereoselectivity (10:1)[15] and in 64% yield over the two steps while rearrangement of the carbon analogue gives only a 2:1 mixture of diastereomers in a similar yield (entries 1 and 2).[16] Rearrangement of allylic trichloroacetimidate **9** gave a similar result as the hydroxy compound **7** (Scheme 3), producing the corresponding allylic amides in a diastereomeric ratio of 5:1 (entry 3). Substrate **10** with the oxygen atom at the 7-position was unable to direct the rearrangement giving the allylic amides in a 2:1 ratio (entry 4). Like the carbon analogue, the *syn* diastereomer **b** was the major product from this reaction.[16]

These results clearly show that without an oxygen atom immediately adjacent to the alkene (i.e., at the 5-position), the diastereoselective outcome of the reaction is particularly low. In the case of the carbon analogue (entry 2), which cannot direct the reaction due to having no oxygen atoms to coordinate to the catalyst, the reaction can only be controlled by steric hindrance. Thus, the catalyst binds directly to the least hindered front face of the alkene (Fig. 2). This forces the acetimidate nitrogen to attack the activated alkene from the back face eventually forming the *syn* diastereomer **b** as the major product. The same ratio of diastereomers obtained for allylic trichloroacetimidate **10** also suggests that this rearrangement is controlled by steric hindrance. Both the hydroxy analogue **7** (Scheme 3) and allylic trichloroacetimidate **9** (entry 3) give similar intermediate ratios of



Scheme 5. Reagents and conditions: (a) Na, MeOH, Δ, 51%; (b) NEt_3, MeOCOCl, THF, then (1*R*,2*R*)-(−)-pseudoephedrine **17**, 97%; (c) LDA, LiCl, MeI, 65%; (d) $LiAlH(OEt)_3$, THF; (e) triethyl phosphonoacetate, LiCl, DBU, MeCN, 21% from **19**; (f) DIBAL-H (2.2 equiv), Et_2O, −78 °C–rt, 87%; (g) DBU, Cl_3CCN, CH_2Cl_2.

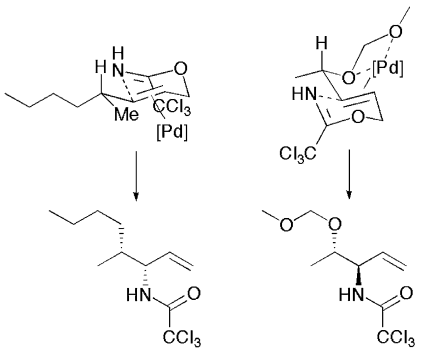
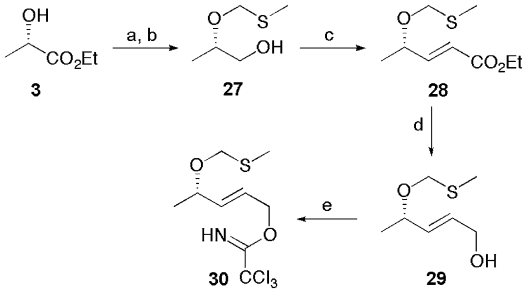


Figure 2. Transition states for the non-coordinating and MOM-ether directed aza-Claisen rearrangement.

diastereomers 4:1 and 5:1, respectively. As the *anti*-diastereomer **a** is now the major product from these rearrangements, this effectively demonstrates that the oxygen atom at the 5-position is coordinating to the palladium(II) catalyst and directing it to the back face of the alkene as depicted in Scheme 2. More importantly, the fact that **7** and **9**, which are very different in size but still rearrange with similar selectivity supports the concept that these rearrangements are controlled by a directing effect and not by steric bulk. The highly selective formation of the *anti*-diastereomer **a** observed for the MOM-substrate **1** again shows that with an oxygen atom at the 5-position the rearrangement is controlled by a directing effect. However, as the selectivity is much higher than for allylic trichloroacetimidates **7** and **9**, we believe that the second oxygen atom assists in coordinating the palladium(II) catalyst resulting in a highly diastereoselective process (Fig. 2). It should be emphasised that all four substrates presented in Table 1 contain the same length of side chain and thus are very similar in size. Yet, when subjected to a palladium(II)-catalysed Overman rearrangement these give the corresponding allylic amides in very different diastereomeric ratios. We believe this study provides strong evidence that chiral allylic trichloroacetimidates with heteroatoms adjacent to the alkene do direct the stereoselective outcome of the rearrangement.[17]

Using the knowledge that both oxygen atoms of the MOM-ether are involved in directing the catalyst, we have briefly attempted to investigate whether different heteroatoms can effect a highly selective rearrangement. Thus, we synthesised a thio-analogue of substrate **1** (Scheme 6) with the expectation that inclusion of a sulfur atom may lead to stronger binding to the palladium(II) catalyst and an enhancement of diastereoselectivity. Alkylation of ethyl (*S*)-lactate **3** with chloromethylmethyl sulfide in the presence of silver nitrate gave the corresponding methylthiomethyl (MTM) ether in 21% yield.[18d] While there are efficient procedures for the formation of MTM ethers from primary[18a,18b] and tertiary alcohols,[18c] their synthesis from secondary alcohols is known to be difficult.[18d] Nevertheless, carried out on a large scale the procedure involving silver nitrate gave enough of the desired product to complete the synthesis of the allylic trichloroacetimidate. The MTM protected lactate was then converted to allylic trichloroacetimidate **30** using our standard approach for the synthesis of these compounds via the (*E*)-α,β-unsaturated ester **28**. Surprisingly, rearrangement of **30** with bis(acetonitrile)palladium(II) chloride resulted in slow decomposition of the allylic trichloroacetimidate. We and others have shown that rearrangement of allylic trichloracetimidates can also be catalysed by gold and platinum complexes.[8b,19] Thus, **30** was also treated with platinum(II) chloride and hydrogen tetrachloroaurate(III) hydrate. However, both these reactions again showed only a slow decomposition of **30**. Thioethers are known to poison heterogeneous catalysts and this may be the case with allylic trichloroacetimidate **30**.[20]



Scheme 6. Reagents and conditions: (a) $AgNO_2$, CH_3SCH_2Cl, NEt_3, THF, 21%; (b) DIBAL-H (2.2 equiv), Et_2O, −78 °C–rt, 82%; (c) DMSO, $(COCl)_2$, NEt_3, CH_2Cl_2, −78 °C–rt, then triethyl phosphonoacetate, LiCl, DBU, MeCN, 37%; (d) DIBAL-H (2.2 equiv), Et_2O, −78 °C–rt, 75%; (e) DBU, Cl_3CCN, CH_2Cl_2.

3. Conclusion

In conclusion, rearrangement of a series of chiral δ-substituted allylic trichloroacetimidates has shown that the diastereoselective outcome of the reaction is controlled by the directing effect of an oxygen atom at the 5-position and not by the steric bulk of the molecule. Moreover, the inclusion of a second oxygen atom further along the side chain as with the MOM-derived substrate **1**, enhances this directing effect leading to a highly diastereoselective process. Further investigation of other heteroatoms for directed rearrangements and the application of the MOM-directed rearrangement for the synthesis of piperidine alkaloids is currently underway.

4. Experimental

4.1. General methods

All reactions were performed under a nitrogen atmosphere unless otherwise noted. Reagents and starting materials were obtained from commercial sources and used as received. THF and diethyl ether were distilled from sodium and benzophenone. Lithium chloride was oven dried (100 °C) for at least 12 h before use. Brine refers to a saturated solution of sodium chloride. Flash column chromatography was carried out using Fisher Matrex silica 60. Macherey-Nagel aluminium backed plates pre-coated with silica gel 60 (UV_{254}) were used for thin layer chromatography and were visualised by staining with $KMnO_4$. ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker DPX 400 spectrometer with chemical shift values in parts per million relative to residual chloroform (δ_H 7.28 and δ_C 77.2) as standard. Infrared spectra were recorded using Golden Gate apparatus on a JASCO FTIR 410 spectrometer and mass spectra were obtained using a JEOL JMS-700 spectrometer. Optical rotations were

determined as solutions irradiating with the sodium D line (λ=589 nm) using an AA series Automatic polarimeter. $[\alpha]_D$ values are given in units 10^{-1} deg cm^2 g^{-1}.

4.1.1. Ethyl (2*S*)-(*tert*-butyldimethylsilyloxy)propanoate.[21] $[\alpha]_D^{20}$ −31.1 (*c* 1.0, $CHCl_3$) (lit.[21] $[\alpha]_D^{20}$ −28.2 (*c* 0.62, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.00 (3H, s, $SiCH_3$), 0.03 (3H, s, $SiCH_3$), 0.89 (9H, s, $Si(CH_3)_3$), 1.26 (3H, t, *J* 7.2 Hz, OCH_2CH_3), 1.38 (3H, d, *J* 6.8 Hz, 3-H_3), 4.16 (2H, m, OCH_2CH_3), 4.30 (1H, q, *J* 6.8 Hz, 2-H); δ_C (100 MHz, $CDCl_3$) −5.0 (CH_3), −4.7 (CH_3), 14.5 (CH_3), 18.6 (C), 21.6 (CH_3), 26.0 (CH_3), 60.9 (CH_2), 68.7 (CH), 174.3 (C).

4.1.2. (2*S*)-*tert*-Butyldimethylsilyloxypropan-1-ol (4).[22] $[\alpha]_D^{23}$ +27.8 (*c* 1.0, $CHCl_3$) (lit.[22] enantiomer, $[\alpha]_D^{25}$ −23.1 (*c* 1.2, $CHCl_3$)); δ_H (400 MHz, $CDCl_3$) 0.11 (6H, s, $Si(CH_3)_2$), 0.92 (9H, s, $Si(CH_3)_3$), 1.14 (3H, d, *J* 6.4 Hz, 3-H_3), 1.94 (1H, dd, *J* 7.6, 5.0 Hz, OH), 3.39 (1H, ddd, *J* 11.2, 6.8, 5.0 Hz, 1-*H*H), 3.52 (1H, ddd, *J* 11.2, 7.6, 3.6 Hz, 1-H*H*), 3.94 (1H, m, 2-H); δ_C (100 MHz, $CDCl_3$) −4.8 (CH_3), −4.4 (CH_3), 18.1 (C), 19.8 (CH_3), 25.8 (CH_3), 68.2 (CH_2), 69.1 (CH).

4.1.3. Ethyl (2*E*,4*S*)-4-(*tert*-butyldimethylsilyloxy)pent-2-enoate (5).[23] $[\alpha]_D^{21}$ +4.4 (*c* 1.0, $CHCl_3$) (lit.[23] $[\alpha]_D^{22}$ +4.4 (*c* 1.2, $CHCl_3$)); δ_H (400 MHz, $CDCl_3$) 0.08 (3H, s, $SiCH_3$), 0.09 (3H, s, $SiCH_3$), 0.93 (9H, s, $Si(CH_3)_3$), 1.28 (3H, d, *J* 6.4 Hz, 5-H_3), 1.31 (3H, t, *J* 7.2 Hz, OCH_2CH_3), 4.21 (2H, m, OCH_2CH_3), 4.47 (1H, m, 4-H), 6.00 (1H, dd, *J* 15.6, 2.0 Hz, 2-H), 6.94 (1H, dd, *J* 15.6, 4.0 Hz, 3-H); δ_C (100 MHz, $CDCl_3$) −4.9 (CH_3), 14.3 (CH_3), 18.2 (C), 23.6 (CH_3), 25.8 (CH_3), 60.3 (CH_2), 67.7 (CH), 119.0 (CH), 151.9 (CH), 166.9 (C).

4.1.4. (2*E*,4*S*)-4-(*tert*-Butyldimethylsilyloxy)-2-penten-1-ol (6).[24] $[\alpha]_D^{23}$ +5.9 (*c* 1.0, $CHCl_3$) (lit.[24] $[\alpha]_D^{19}$ +3.7 (*c* 2.9, $CHCl_3$)); δ_H (400 MHz, $CDCl_3$) 0.08 (3H, s, $SiCH_3$), 0.09 (3H, s, $SiCH_3$), 0.92 (9H, s, $Si(CH_3)_3$), 1.24 (3H, d, *J* 6.3 Hz, 5-H_3), 1.43 (1H, br s, OH), 4.16 (2H, d, *J* 6.0 Hz, 1-H_2), 4.27 (1H, m, 4-H), 5.72–5.84 (2H, m, 2-H and 3-H); δ_C (100 MHz, $CDCl_3$) −4.4 (CH_3), −4.2 (CH_3), 18.7 (C), 24.7 (CH_3), 26.3 (CH_3), 63.6 (CH_2), 68.9 (CH), 127.6 (CH) and 136.8 (CH).

4.1.5. (3*R*,4*S*)-3-Trichloromethylcarbonylamino-4-hydroxypenta-1-ene (8a) and (3*S*,4*S*)-3-trichloromethylcarbonylamino-4-hydroxypenta-1-ene (8b). (2*E*,4*S*)-4-(*tert*-Butyldimethylsilyloxy)-2-penten-1-ol (0.8 g, 3.7 mmol) was dissolved in dichloromethane (20 mL) and cooled to 0 °C. 1,8-Diazabicyclo[5,4,0]undec-7-ene (0.6 mL, 4.4 mmol) and trichloroacetonitrile (0.6 mL, 5.6 mmol) were then added and the mixture was allowed to warm to room temperature and stirred for 2 h. The reaction mixture was then filtered through a silica plug and the filtrate was concentrated in vacuo to give an orange liquid. The allylic trichloroacetimidate and tetra-*n*-butylammonium fluoride (TBAF) (1 M soln in tetrahydrofuran) (6.7 mL, 6.7 mmol) in THF (20 mL) were allowed to stir at room temperature for 24 h. The reaction mixture was concentrated and the resulting residue was taken up in ethyl acetate (30 mL), washed with water (25 mL), dried ($MgSO_4$) and concentrated in vacuo. The product was used without further purification. The allylic trichloroacetimidate was dissolved in THF (10 mL). Bis(acetonitrile)palladium(II) chloride (10 mol %) was then added and the reaction mixture stirred for 24 h. Concentration in vacuo followed by purification by flash column chromatography (40% ethyl acetate/petroleum ether) gave **8a** and **8b** (0.28 g, 31% over three steps) as a yellow oil, in a ratio of 4:1. ν_{max}/cm^{-1} (neat): 3403 (OH, NH), 2979 (CH), 1693 (CO); **8a**: δ_H (400 MHz, $CDCl_3$) 1.27 (3H, d, *J* 6.4 Hz, 5-H_3), 1.97 (1H, br d, *J* 5.6 Hz, OH), 4.05 (1H, m, 4-H), 4.38 (1H, m, 3-H), 5.39 (2H, m, 1-H_2), 5.90 (1H, m, 2-H), 7.24 (1H, br s, NH); δ_C (100 MHz, $CDCl_3$) 20.0 (CH_3), 58.6 (CH), 68.9 (CH), 92.7 (C), 119.6 (CH_2), 131.1 (CH), 161.4 (C); **8b**: δ_H (400 MHz, $CDCl_3$) 1.29 (3H, d, *J* 6.4 Hz, 5-H_3), 2.04 (1H, br s, OH), 4.05 (1H, m, 4-H), 4.38 (1H, m, 3-H), 5.33 (2H, m, 1-H_2), 5.90 (1H, m, 2-H), 7.13 (1H, br s, NH); δ_C (100 MHz, $CDCl_3$) 20.0 (CH_3), 58.2 (CH), 68.6 (CH), 92.7 (C), 117.4 (CH_2), 134.7 (CH), 162.0 (C); found (CI): MH^+, 247.9825, $C_7H_{10}O_2N^{35}Cl_2{}^{37}Cl$ requires MH^+, 247.9826.

4.1.6. Ethyl (2*S*)-2-(propyloxy-2-ene)propanoate.[25] $[\alpha]_D^{25}$ −67.8 (*c* 2.0, MeOH) (lit.[25] $[\alpha]_D^{25}$ −70.7 (*c* 2.7, MeOH)); δ_H (400 MHz, $CDCl_3$) 1.31 (3H, t, *J* 7.2 Hz, OCH_2CH_3), 1.44 (3H, d, *J* 6.8 Hz, 3-H_3), 3.96 (1H, ddt, *J* 12.8, 6.8, 1.2 Hz, OC*H*HCHCH$_2$), 4.02 (1H, q, *J* 6.8 Hz, 2-H), 4.16 (1H, ddt, *J* 12.8, 5.6, 1.2 Hz, OCH*H*CHCH$_2$), 4.23 (2H, m, OCH_2CH_3), 5.20–5.34 (2H, m, OCH_2CHCH_2), 5.89–5.99 (1H, m, OCH_2CHCH_2); δ_C (100 MHz, $CDCl_3$) 14.3 (CH_3), 18.7 (CH_3), 60.8 (CH_2), 71.1 (CH_2), 74.1 (CH), 117.7 (CH_2), 134.2 (CH), 173.3 (C).

4.1.7. Ethyl (2*S*)-2-propyloxypropanoate (11).[26] $[\alpha]_D^{25}$ −98.3 (neat) (lit.[26] $[\alpha]_D^{20}$ −100.9 (neat)); δ_H (400 MHz, $CDCl_3$) 0.95 (3H, t, *J* 7.2 Hz, $OCH_2CH_2CH_3$), 1.31 (3H, t, *J* 7.2 Hz, OCH_2CH_3), 1.42 (3H, d, *J* 6.8 Hz, 3-H_3), 1.64 (2H, sex, *J* 7.2 Hz, $OCH_2CH_2CH_3$), 3.34 (1H, dt, *J* 8.8, 7.2 Hz, OC*H*HCH$_2$CH$_3$), 3.54 (1H, dt, *J* 8.8, 7.2 Hz, OCH*H*CH$_2$CH$_3$), 3.96 (1H, q, *J* 6.8 Hz, 2-H), 4.22 (2H, m, OCH_2CH_3); δ_C (100 MHz, $CDCl_3$) 10.5 (CH_3), 14.3 (CH_3), 18.7 (CH_3), 23.0 (CH_2), 60.7 (CH_2), 72.0 (CH_2), 75.0 (CH), 173.6 (C).

4.1.8. (2*S*)-Propyloxypropan-1-ol (12).[27] $[\alpha]_D^{24}$ +17.8 (*c* 1.0, $CHCl_3$) (lit.[27] $[\alpha]_D^{25}$ +26.1 (neat)); δ_H (400 MHz, $CDCl_3$) 0.94 (3H, t, *J* 7.6 Hz, $OCH_2CH_2CH_3$), 1.12 (3H, d, *J* 6.0 Hz, 3-H_3), 1.61 (2H, m, $OCH_2CH_2CH_3$), 2.08 (1H, br s, OH), 3.34 (1H, dt, *J* 8.8, 6.8 Hz, OC*H*HCH$_2$CH$_3$), 3.41–3.61 (4H, m, 1-H_2, 2-H and OCH*H*CH$_2$CH$_3$); δ_C (100 MHz, $CDCl_3$) 10.6 (CH_3), 15.9 (CH_3), 23.3 (CH_2), 66.4 (CH_2), 70.5 (CH_2), 75.7 (CH).

4.1.9. Ethyl (2*E*,4*S*)-4-propyloxypent-2-enoate (13). Methyl sulfoxide (2.6 mL, 36.6 mmol) was added to a stirred solution of oxalyl chloride (1.6 mL, 18.3 mmol) in dichloromethane (50 mL) at −78 °C. This mixture was stirred for 0.25 h before (2*S*)-propyloxypropan-1-ol (1.8 g, 15.3 mmol) in dichloromethane (30 mL) was added. The mixture was stirred for a further 0.25 h before triethylamine (10.6 mL, 76.3 mmol) was added. This reaction mixture was then warmed to room temperature over 2 h. Meanwhile, a solution of lithium chloride (0.97 g, 22.9 mmol), triethyl phosphonoacetate (4.5 mL, 22.9 mmol) and 1,8-diazabicyclo[5,4,0]-undec-7-ene (3.4 mL, 22.9 mmol) in acetonitrile (30 mL) was prepared and stirred for 0.5 h at room temperature.

The HWE mixture was added to the Swern solution and the reaction mixture was allowed to stir at room temperature overnight. The reaction was quenched with brine (50 mL) and then concentrated to give an orange residue. This residue was extracted with diethyl ether (5×50 mL) and the organic layers were combined, dried ($MgSO_4$) and concentrated to give an orange oil. Purification was carried out by flash column chromatography (40% diethyl ether/petroleum ether) to give **13** (1.15 g, 41%) as a colourless oil. ν_{max}/cm^{-1} (neat): 2977 (CH), 1719 (CO), 1658 (C=C), 1271, 1180, 1097, 982; $[\alpha]_D^{24}$ −10.0 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.94 (3H, t, *J* 7.0 Hz, $OCH_2CH_2CH_3$), 1.30 (3H, d, *J* 6.4 Hz, 5-H_3), 1.32 (3H, t, *J* 7.2 Hz, OCH_2CH_3), 1.61 (2H, sex, *J* 7.0 Hz, $OCH_2CH_2CH_3$), 3.34 (1H, dt, *J* 8.8, 7.0 Hz, $OCHHCH_2CH_3$), 3.41 (1H, dt, *J* 8.8, 7.0 Hz, $OCHHCH_2CH_3$), 4.01 (1H, quin d, *J* 6.4, 1.2 Hz, 4-H), 4.22 (2H, q, *J* 7.2 Hz, OCH_2CH_3), 5.99 (1H, dd, *J* 15.6, 1.2 Hz, 2-H), 6.87 (1H, dd, *J* 15.6, 6.4 Hz, 3-H); δ_C (100 MHz, $CDCl_3$) 10.6 (CH_3), 14.3 (CH_3), 20.7 (CH_3), 23.1 (CH_2), 60.4 (CH_2), 70.8 (CH_2), 74.6 (CH), 120.8 (CH), 149.8 (CH), 166.5 (C); found (CI): MH^+, 187.1336, $C_{10}H_{18}O_3$ requires MH^+, 187.1334.

4.1.10. (2*E*,4*S*)-4-Propyloxypent-2-en-1-ol (14). Ethyl (2*E*,4*S*)-4-propyloxypent-2-enoate (1.1 g, 5.8 mmol) was dissolved in diethyl ether (50 mL) and cooled to −78 °C. DIBAL-H (1 M in hexane) (12.7 mL, 12.7 mmol) was added dropwise and the reaction mixture was allowed to stir at −78 °C for 4 h. The reaction was quenched by the addition of a saturated solution of ammonium chloride (10 mL) and warmed to room temperature producing a white precipitate. The precipitate was filtered through a pad of Celite® and washed with diethyl ether (3×100 mL). The filtrate was then dried ($MgSO_4$) and concentrated in vacuo. Purification was carried out by flash column chromatography (50% diethyl ether/petroleum ether) to give **14** (0.55 g, 66%). ν_{max}/cm^{-1} (neat): 3367 (OH), 2970 (CH), 1653 (C=C), 1558, 1541, 1456, 1086 and 971; $[\alpha]_D^{24}$ −11.0 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.93 (3H, t, *J* 7.2 Hz, $OCH_2CH_2CH_3$), 1.26 (3H, d, *J* 6.4 Hz, 5-H_3), 1.41 (1H, t, *J* 6.4 Hz, OH), 1.60 (2H, sex, *J* 7.2 Hz, $OCH_2CH_2CH_3$), 3.30 (1H, dt, *J* 8.8, 7.2 Hz, $OCHHCH_2CH_3$), 3.42 (1H, dt, *J* 8.8, 7.2 Hz, $OCHHCH_2CH_3$), 3.88 (1H, quin, *J* 6.4 Hz, 4-H), 4.18 (2H, m, 1-H_2), 5.66 (1H, ddt, *J* 15.2, 6.4, 1.2 Hz, 3-H), 5.81 (1H, dt, *J* 15.2, 5.6 Hz, 2-H); δ_C (100 MHz, $CDCl_3$) 10.6 (CH_3), 21.3 (CH_3), 23.1 (CH_2), 63.1 (CH_2), 70.1 (CH_2), 75.5 (CH), 130.2 (CH), 134.0 (CH); found (CI): MH^+, 145.1223, $C_8H_{16}O_2$ requires MH^+, 145.1229.

4.1.11. (3*R*,4*S*)-3-Trichloromethylcarbonylamino-4-propyloxypenta-1-ene (25a) and (3*S*,4*S*)-3-trichloromethylcarbonylamino-4-propyloxypenta-1-ene (25b). (2*E*,4*S*)-4-Propyloxypent-2-en-1-ol (0.2 g, 1.4 mmol) was dissolved in dichloromethane (20 mL) and cooled to 0 °C. 1,8-Diazabicyclo[5,4,0]undec-7-ene (0.3 mL, 1.7 mmol) and trichloroacetonitrile (0.2 mL, 2.1 mmol) were then added and the mixture was allowed to warm to room temperature and stir for 2 h. The reaction mixture was then filtered through a silica plug and the filtrate was concentrated in vacuo to give an orange oil. The allylic trichloroacetimidate was dissolved in THF (10 mL). Bis(acetonitrile)palladium(II) chloride (31 mg, 10 mol %) was then added and the reaction mixture stirred for 24 h. Concentration in vacuo followed by purification by flash column chromatography (30% diethyl ether/petroleum ether) gave **25a** and **25b** (0.25 g, 77%) as a colourless oil in a ratio of 5:1. ν_{max}/cm^{-1} (neat): 3331 (NH), 2931 (CH), 1715 (CO), 1652 (C=C), 1518, 1114 and 822; **25a**: δ_H (400 MHz, $CDCl_3$) 0.96 (3H, t, *J* 7.7 Hz, $OCH_2CH_2CH_3$), 1.18 (3H, d, *J* 6.4 Hz, 5-H_3), 1.54–1.65 (2H, m, $OCH_2CH_2CH_3$), 3.29 (1H, dt, *J* 8.8, 6.4 Hz, $OCHHCH_2CH_3$), 3.62–3.67 (2H, m, 4-H and $OCHHCH_2CH_3$), 4.32–4.39 (1H, m, 3-H), 5.31–5.36 (2H, m, 1-H_2), 5.82–5.91 (1H, m, 2-H); δ_C (100 MHz, $CDCl_3$) 10.8 (CH_3), 16.0 (CH_3), 23.1 (CH_2), 57.9 (CH), 70.8 (CH_2), 75.8 (CH), 92.5 (C), 119.2 (CH_2), 131.8 (CH), 161.0 (C). **25b**: δ_H (400 MHz, $CDCl_3$) 0.93 (3H, t, *J* 7.6 Hz, $OCH_2CH_2CH_3$), 1.21 (3H, d, *J* 6.4 Hz, 5-H_3), 1.57–1.66 (2H, m, $OCH_2CH_2CH_3$), 3.34 (1H, dt, *J* 8.8, 6.4 Hz, $OCHHCH_2CH_3$), 3.54–3.60 (1H, m, 4-H), 4.32–4.39 (1H, m, 3-H), 5.23–5.28 (2H, m, 1-H_2), 5.87–5.95 (1H, m, 2-H); δ_C (100 MHz, $CDCl_3$) 10.7 (CH_3), 17.0 (CH_3), 23.1 (CH_2), 58.1 (CH), 71.1 (CH_2), 75.8 (CH), 88.4 (C), 116.9 (CH_2), 135.1 (CH), 161.4 (C); found (CI): MH^+, 288.0328, $C_{10}H_{16}O_2N^{35}Cl_3$ requires MH^+, 288.0325.

4.1.12. 4-Methoxybutanoic acid (16).[28] δ_H (400 MHz, $CDCl_3$) 1.90 (2H, m, 3-H_2), 2.48 (2H, t, *J* 7.2 Hz, 2-H_2), 3.36 (3H, s, OMe), 3.45 (2H, t, *J* 6.0 Hz, 4-H_2); δ_C (100 MHz, $CDCl_3$) 24.6 (CH_3), 30.8 (CH_2), 58.6 (CH_3), 71.5 (CH_2), 178.9 (C).

4.1.13. (1′*R*,2′*R*)-*N*-(2′-Hydroxy-1′-methyl-2′-phenylethyl)-4-methoxy-*N*-methyl-butyramide (18). 4-Methoxybutanoic acid (2.36 g, 20.0 mmol) was dissolved in THF (50 mL) and cooled to 0 °C. Triethylamine (3.1 mL, 22.0 mmol) and methyl chloroformate (1.7 mL, 22.0 mmol) were then added producing a white precipitate. This suspension was stirred for 1 h before a solution of (1*R*,2*R*)-(−)-pseudoephedrine (3.63 g, 22.0 mmol) in THF (20 mL) was added and the mixture was allowed to stir at room temperature for 12 h. The reaction was quenched with brine (50 mL), concentrated and then extracted with ethyl acetate (3×50 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo to give a clear liquid. Purification was carried out by flash column chromatography (50% ethyl acetate/petroleum ether) to give **18** (5.1 g, 97%) as a clear oil. ν_{max}/cm^{-1} (neat) 3390 (OH), 2932 (CH), 1623 (CO), 1453 (C=C), 1118, 756, 703; $[\alpha]_D^{21}$ −91.8 (*c* 1.0, $CHCl_3$); compound **18** exists as a 3:1 mixture of rotamers, signals for major rotamer are: δ_H (400 MHz, $CDCl_3$) 1.12 (3H, d, *J* 6.8 Hz, 1′-CH_3), 1.92 (2H, m, 3-H_2), 2.40 (2H, m, 2-H_2), 2.85 (3H, s, NMe), 3.34 (3H, s, OMe), 3.43 (2H, t, *J* 6.0 Hz, 4-H_2), 4.27 (1H, br s, 2′-OH), 4.47 (1H, m, 1′-H), 4.56–4.63 (1H, m, 2′-H), 7.33–4.40 (5H, m, Ph); δ_C (100 MHz, $CDCl_3$) 14.5 (CH_3), 25.1 (CH_2), 30.9 (CH_2), 58.6 (CH_3), 71.8 (CH_2), 76.6 (CH_3), 126.4 (CH), 127.0 (CH), 127.7 (CH), 128.4 (CH), 128.7 (CH), 142.3 (C), 175.1 (C); found (CI): MH^+, 266.1755, $C_{15}H_{23}O_3N$ requires MH^+, 266.1756.

4.1.14. (1′*R*,2*R*,2′*R*)-*N*-(2′-Hydroxy-1′-methyl-2′-phenylethyl)-4-methoxy-2-methyl-*N*-methylbutyramide (19). A solution of lithium chloride (0.09 g, 2.15 mmol) and diisopropylamine (0.11 mL, 0.81 mmol) in THF (5 mL) was cooled to −78 °C before *n*-butyllithium (2.5 M in hexane, 0.3 mL, 0.75 mmol) was added. The solution was warmed

briefly to 0 °C, then was re-cooled to −78 °C and stirred for 0.5 h. A solution of **18** (0.1 g, 0.35 mmol) in THF (10 mL), cooled to 0 °C, was transferred to the reaction flask and the resulting solution was stirred at −78 °C for 1 h, 0 °C for 0.25 h and at room temperature for 0.1 h. The reaction mixture was then cooled to 0 °C, where upon methyl iodide (0.08 mL, 0.54 mmol) was added. After 3 h the reaction was quenched with saturated aqueous ammonium chloride solution (20 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (3×20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated to give a yellow oil. Purification by chromatography (50% ethyl acetate/petroleum ether) gave **19** (0.1 g, 65%) as a yellow liquid. ν_{max}/cm^{-1} (neat) 3364 (OH), 2973 (CH), 1612 (CO), 1451, 1111, 750, 700; $[\alpha]_D^{23}$ −96.2 (*c* 1.0, $CHCl_3$); compound **19** exists as a 3:1 mixture of rotamers, signals for major rotamer are: δ_H (400 MHz, $CDCl_3$) 1.06 (3H, d, *J* 6.8 Hz, 1′-CH_3), 1.13 (3H, d, *J* 6.8 Hz, 2-CH_3), 1.62 (1H, m, 3-*H*H), 1.89–2.05 (2H, m, 2-H and 3-H*H*), 2.87 (3H, s, NMe), 3.31 (3H, s, OMe), 3.38 (2H, m, 4-H_2), 4.45 (1H, br s, OH), 4.55–4.64 (2H, m, 1′-H and 2′-H), 7.35 (5H, m, Ph); δ_C (100 MHz, $CDCl_3$) 14.4 (CH_3), 17.7 (CH_3), 33.4 (CH), 34.1 (CH_2), 58.6 (CH_3), 70.6 (CH_2), 76.3 (CH_3), 126.3 (CH), 126.5 (CH), 127.0 (CH), 127.6 (CH), 128.7 (CH), 142.4 (C), 178.7 (C); found (CI): MH^+, 280.1911, $C_{16}H_{25}O_3N$ requires MH^+, 280.1913.

4.1.15. Ethyl (2*E*,4*R*)-4-methyl-6-methoxyhex-2-enoate (21). Lithium aluminium hydride (0.22 g, 5.86 mmol) was suspended in anhydrous hexanes (20 mL) and cooled to 0 °C. Anhydrous ethyl acetate (0.85 mL, 8.70 mmol) was added dropwise over 0.5 h and the solution was allowed to stir for a further 1 h before being cooled to −78 °C. A solution of **19** (0.71 g, 2.55 mmol) in THF (15 mL) was added to the $LiAlH(OEt)_3$ solution with the evolution of H_2 gas. The reaction mixture was then allowed to stir for 0.25 h at −78 °C, then at 0 °C for 5 h. The reaction was quenched with a solution of trifluoroacetic acid (1.9 mL, 25.5 mmol) in hydrochloric acid solution (1 M, 10 mL). Separation of the organic layer was followed by extraction of the aqueous layer with diethyl ether (3×20 mL). The combined organic layers were then neutralised to pH 7 with sodium hydrogen carbonate solution (30 mL). The aqueous layer was extracted with diethyl ether (2×20 mL) and the combined organic layers were dried ($MgSO_4$). The aldehyde was used without further purification. A solution of lithium chloride (0.16 mg, 3.8 mmol), triethyl phosphonoacetate (0.76 mL, 3.8 mmol) and 1,8-diazabicyclo[5,4,0]undec-7-ene (0.57 mL, 3.8 mmol) in acetonitrile (10 mL) was prepared and stirred for 0.5 h. The ylide mixture was added to the aldehyde solution and the reaction mixture was allowed to stir at room temperature overnight. The reaction was quenched with brine (50 mL) and then concentrated to give an orange residue. This residue was extracted with diethyl ether (5×50 mL) and the organic layers were combined, dried ($MgSO_4$) and concentrated to give an orange oil. Purification by flash column chromatography (50% diethyl ether/petroleum ether) gave **21** (0.07 g, 21% over two steps) as a colourless oil. ν_{max}/cm^{-1} (neat) 2931 (CH), 1719 (CO), 1651 (C=C), 1270, 1179, 1120; $[\alpha]_D^{22}$ −27.5 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.09 (3H, d, *J* 6.8 Hz, 4-CH_3), 1.31 (3H, t, *J* 7.2 Hz, OCH_2CH_3), 1.66 (2H, q, *J* 6.8 Hz, 5-H_2), 2.50 (1H, m, 4-H), 3.33 (3H, s, OMe), 3.35–3.41 (2H, m, 6-H_2), 4.20 (2H, q, *J* 7.2 Hz, OCH_2CH_3), 5.81 (1H, dd, *J* 15.6, 1.2 Hz, 2-H), 6.87 (1H, dd, *J* 15.6, 8.0 Hz, 3-H); δ_C (100 MHz, $CDCl_3$) 14.3 (CH_3), 19.4 (CH_3), 33.3 (CH), 35.7 (CH_2), 58.6 (CH_3), 60.2 (CH_2), 70.3 (CH_2), 120.0 (CH), 153.8 (CH), 166.8 (C); found (CI): MH^+, 187.1329, $C_{10}H_{18}O_3$ requires MH^+, 187.1334.

4.1.16. (2*E*,4*R*)-4-Methyl-6-methoxyhex-2-en-1-ol (22). Ethyl (2*E*,4*R*)-4-methyl-6-methoxyhex-2-enoate (0.8 g, 0.4 mmol) was dissolved in diethyl ether (10 mL) and cooled to −78 °C. DIBAL-H (1 M in hexane) (0.9 mL, 0.9 mmol) was added dropwise and the reaction mixture was allowed to stir at −78 °C for 4 h. The reaction was quenched by the addition of a saturated solution of ammonium chloride (1 mL) and warmed to room temperature producing a white precipitate. The precipitate was filtered through a pad of Celite® and washed with diethyl ether (3×20 mL). The filtrate was then dried ($MgSO_4$) and concentrated in vacuo. Purification was carried out by flash column chromatography (50% diethyl ether/petroleum ether) to give **22** as a colourless oil. ν_{max}/cm^{-1} (neat) 3382 (OH), 2929 (CH), 1456 (C=C), 1116, 972, 669; $[\alpha]_D^{21}$ −22.7 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.03 (3H, d, *J* 6.8 Hz, 4-CH_3), 1.36 (1H, br s, OH), 1.59 (2H, q, *J* 6.4 Hz, 5-H_2), 2.32 (1H, m, 4-H), 3.34 (3H, s, OMe), 3.39 (2H, t, *J* 6.4 Hz, 6-H_2), 4.12 (2H, m, 1-H_2), 5.56–5.68 (2H, m, 2-H and 3-H); δ_C (100 MHz, $CDCl_3$) 20.4 (CH_3), 33.2 (CH), 36.4 (CH_2), 58.6 (CH_3), 63.8 (CH_2), 70.8 (CH_2), 127.6 (CH), 138.2 (CH); found (CI): MH^+-H_2O, 127.1125, $C_8H_{16}O_2$ requires MH^+-H_2O, 127.1123.

4.1.17. (3*R*,4*R*)-3-(Trichloromethylcarbonylamino)-4-methyl-6-methoxyhexa-1-ene (26a) and (3*S*,4*R*)-3-(trichloromethylcarbonylamino)-4-methyl-6-methoxyhexa-1-ene (26b). (2*E*,4*R*)-4-Methyl-6-methoxyhex-2-en-1-ol (0.05 g, 0.4 mmol) was dissolved in dichloromethane (10 mL) and cooled to 0 °C. 1,8-Diazabicyclo[5,4,0]undec-7-ene (0.1 mL, 0.4 mmol) and trichloroacetonitrile (0.1 mL, 0.5 mmol) were then added and the mixture was allowed to warm to room temperature and stirred for 2 h. The reaction mixture was then filtered through a silica plug and the filtrate was concentrated in vacuo to give an orange oil. The product was used without further purification. The allylic trichloroacetimidate was dissolved in THF (10 mL). Bis(acetonitrile)-palladium(II) chloride (9 mg, 10 mol %) was then added and the reaction mixture stirred for 24 h. Concentration in vacuo followed by purification by flash column chromatography eluting with diethyl ether/petroleum ether gave **26a** and **26b** (0.06 mg, 60%) as a brown oil, in a ratio of 1:2. ν_{max}/cm^{-1} (neat) 3331 (NH), 2931 (CH), 1715 (CO), 1652 (C=C), 1518, 1114, 822; **26a**: δ_H (400 MHz, $CDCl_3$) 1.00 (3H, d, *J* 6.8 Hz, 4-CH_3), 1.66 (2H, m, 5-H_2), 1.97 (1H, m, 4-H), 3.37 (3H, s, OMe), 3.45 (2H, m, 6-H_2), 4.39 (1H, m, 3-H), 5.26 (2H, m, 1-H_2), 5.81 (1H, m, 2-H), 7.67 (1H, br d, *J* 7.2 Hz, NH); δ_C (100 MHz, $CDCl_3$) 17.5 (CH_3), 32.6 (CH_2), 35.3 (CH), 57.2 (CH_3), 58.8 (CH), 71.2 (CH), 93.3 (C), 117.0 (CH), 134.3 (CH), 161.4 (C); **26b**: δ_H (400 MHz, $CDCl_3$) 1.02 (3H, d, *J* 6.8 Hz, 4-CH_3), 1.66 (2H, m, 5-H_2), 2.05 (1H, m, 4-H), 3.36 (3H, s, OMe), 3.51 (2H, m, 6-H_2), 4.39 (1H, m, 3-H), 5.22 (2H, m, 1-H_2), 5.79 (1H, m, 2-H), 7.76 (1H, br d, *J* 6.0 Hz, NH); δ_C (100 MHz, $CDCl_3$) 16.3 (CH_3), 31.2 (CH_2), 34.6 (CH), 57.7 (CH_3), 58.9 (CH), 69.5 (CH), 93.3 (C), 116.3 (CH), 135.9 (CH),

161.7 (C). Anal. Calcd for $C_{10}H_{16}O_2NCl_3$: C, 41.62; H, 5.59; N, 4.85. Found: C, 41.70; H, 5.58; N, 4.74; *m/z* (CI) 290 (MH^+, 89%), 254 (20), 220 (36), 218 (100) and 184 (8).

4.1.18. Ethyl (2*S*)-2-(methylsulfanylmethoxy)propanoate. A solution of ethyl (*S*)-lactate (0.50 g, 4.24 mmol) and chloromethylmethyl sulfide (0.43 g, 5.09 mmol) in THF (15 mL) was added to a solution of silver nitrate (0.79 g, 4.66 mmol) and triethylamine (0.71 mL, 5.09 mmol) in THF (10 mL). The reaction mixture was allowed to stir at room temperature for 4 h before being heated to 80 °C and stirred for five days. The mixture was filtered through Celite® and then washed with saturated ammonium chloride solution (20 mL), saturated sodium hydrogen carbonate solution (20 mL) and water (20 mL). The organic layer was then dried ($MgSO_4$) and concentrated to give a brown oil. Purification was carried out by flash column chromatography (30% diethyl ether/petroleum ether) to give ethyl (2*S*)-2-(methylsulfanylmethoxy)propanoate (0.16 g, 21%). ν_{max}/cm^{-1} (neat) 2984 (CH), 1746 (CO), 1201, 1109, 1063, 1024; $[\alpha]_D^{21}$ −166.0 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.31 (3H, t, *J* 7.2 Hz, OCH_2CH_3), 1.44 (3H, d, *J* 7.0 Hz, 3-H_3), 2.18 (3H, s, SMe), 4.22 (2H, qd, *J* 7.2, 1.2 Hz, OCH_2CH_3), 4.37 (1H, q, *J* 7.0 Hz, 2-H), 4.66 (1H, d, *J* 11.6 Hz, OC*H*HS), 4.79 (1H, d, *J* 11.6 Hz, OCH*H*S); δ_C (100 MHz, $CDCl_3$) 14.0 (CH_3), 14.2 (CH_3), 18.4 (CH_3), 61.0 (CH_2), 71.2 (CH), 74.3 (CH_2), 172.9 (C); found (CI): MH^+, 179.0740, $C_7H_{14}O_3S$ requires MH^+, 179.0742.

4.1.19. (2*S*)-2-(Methylsulfanylmethoxy)propan-1-ol (27). Ethyl (2*S*)-2-(methylsulfanylmethoxy)propanoate (1.58 g, 8.87 mmol) was dissolved in diethyl ether (50 mL) and cooled to −78 °C. DIBAL-H (1 M in hexane) (19.5 mL, 19.5 mmol) was added dropwise and the reaction mixture was allowed to stir at −78 °C for 1 h, then overnight at room temperature. The reaction mixture was cooled to 0 °C before being quenched by the addition of a saturated solution of ammonium chloride (10 mL) and warmed to room temperature producing a white precipitate. The reaction mixture was filtered through a pad of Celite® and washed with diethyl ether (3×50 mL). The filtrate was then dried ($MgSO_4$) and concentrated in vacuo. Purification by flash column chromatography (40% diethyl ether/petroleum ether) gave **27** (753 mg, 82%) as colourless oil. ν_{max}/cm^{-1} (neat) 3418 (OH), 2922 (CH), 1436, 1301, 1060, 681; $[\alpha]_D^{19}$ +146.9 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.16 (3H, d, *J* 6.4 Hz, 3-H_3), 2.13 (1H, m, OH), 2.20 (3H, s, SMe), 3.52 (1H, dd, *J* 11.6, 6.8 Hz, 1-*H*H), 3.64 (1H, dd, *J* 11.6, 3.2 Hz, 1-H*H*), 3.90 (1H, m, 2-H), 4.65 (1H, d, *J* 11.2 Hz, OC*H*HS), 4.77 (1H, d, *J* 11.2 Hz, OCH*H*S); δ_C (100 MHz, $CDCl_3$) 14.0 (CH_3), 15.9 (CH_3), 66.2 (CH_2), 73.3 (CH_2), 74.0 (CH); *m/z* (CI) 137 (MH^+, 50%), 118 (10), 105 (21) and 89 (100).

4.1.20. Ethyl (2*E*,4*S*)-4-(methylsulfanylmethoxy)pent-2-enoate (28). Methyl sulfoxide (0.9 mL, 12.7 mmol) was added to a stirred solution of oxalyl chloride (0.56 mL, 6.36 mmol) in dichloromethane (25 mL) at −78 °C. This mixture was stirred for 0.25 h before **27** (0.55 g, 5.28 mmol) in dichloromethane (25 mL) was added. The mixture was stirred for a further 0.25 h before triethylamine (3.7 mL, 26.4 mmol) was added. This reaction mixture was then allowed to stir for 2 h. In a second flask, a solution of lithium chloride (0.34 g, 7.93 mmol), triethyl phosphonoacetate (1.6 mL, 7.93 mmol) and 1,8-diazabicyclo[5,4,0]undec-7-ene (1.2 mL, 7.93 mmol) in acetonitrile (30 mL) was prepared and stirred for 0.5 h. The contents of the second flask were then added to the Swern solution and the reaction mixture was allowed to stir at room temperature overnight. The reaction was quenched with brine (40 mL) and then concentrated in vacuo. This residue was extracted with diethyl ether (5×30 mL) and the organic layers were combined, dried ($MgSO_4$) and concentrated to give an orange oil. Purification was carried out by flash column chromatography (30% diethyl ether/petroleum ether) to give **28** (0.4 g, 37%) as colourless oil. ν_{max}/cm^{-1} (neat) 2980 (CH), 1716 (CO), 1659 (C=C), 1300, 1266, 1180, 1051; $[\alpha]_D^{21}$ −232.4 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.29–1.33 (6H, m, OCH_2CH_3 and 5-H_3), 2.17 (3H, s, MeS), 4.22 (2H, q, *J* 6.8 Hz, OCH_2CH_3), 4.48 (1H, quin d, *J* 6.2, 1.6 Hz, 4-H), 4.55 (1H, d, *J* 11.6 Hz, OC*H*HS), 4.70 (1H, d, *J* 11.6 Hz, OCH*H*S), 6.01 (1H, dd, *J* 15.6, 1.6 Hz, 2-H), 6.84 (1H, dd, *J* 15.6, 6.2 Hz, 3-H); δ_C (100 MHz, $CDCl_3$) 13.8 (CH_3), 14.3 (CH_3), 20.3 (CH_3), 60.5 (CH_2), 70.9 (CH), 72.8 (CH_2), 121.6 (CH), 148.4 (CH), 166.3 (C); found (CI): MH^+, 205.0896, $C_9H_{16}O_3S$ requires MH^+, 205.0898.

4.1.21. (2*E*,4*S*)-(Methylsulfanylmethoxy)pent-2-en-1-ol (29). Ethyl (2*E*,4*S*)-4-methylsulfanylmethoxypent-2-enoate (0.34 g, 1.79 mmol) was dissolved in diethyl ether (20 mL) and cooled to −78 °C. DIBAL-H (1 M in hexane) (4.0 mL, 3.95 mmol) was added dropwise and the reaction mixture was allowed to stir at −78 °C for 2 h and then overnight at room temperature. The reaction mixture was cooled to 0 °C, quenched by the addition of a saturated solution of ammonium chloride (2 mL) and warmed to room temperature. The precipitate was filtered through a pad of Celite® and washed with diethyl ether (3×20 mL). The filtrate was then dried ($MgSO_4$) and concentrated in vacuo. Purification was carried out by flash column chromatography using (50% diethyl ether/petroleum ether) to give **29** (0.22 g, 75%) as a colourless oil. ν_{max}/cm^{-1} (neat) 3403 (OH), 2975 (CH), 1671 (C=C), 1433, 1374, 1300, 1057; $[\alpha]_D^{21}$ −250.3 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.29 (3H, t, *J* 6.4 Hz, 5-H_3), 1.47 (1H, br s, OH), 2.18 (3H, s, SMe), 4.19 (2H, dd, *J* 5.2, 1.6 Hz, 1-H_2), 4.33 (1H, m, 4-H), 4.55 (1H, d, *J* 11.6 Hz, OC*H*HS), 4.67 (1H, d, *J* 11.6 Hz, OCH*H*S), 5.63 (1H, ddt, *J* 15.6, 7.6, 1.6 Hz, 3-H), 5.86 (1H, dtd, *J* 15.6, 5.2, 0.8 Hz, 2-H); δ_C (100 MHz, $CDCl_3$) 13.8 (CH_3), 21.1 (CH_3), 62.9 (CH_2), 72.0 (CH_2), 72.1 (CH), 131.7 (CH), 132.3 (CH); found (CI): MH^+-H_2O, 145.0685, $C_7H_{14}O_2S$ requires MH^+-H_2O, 145.0688.

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16. In the case of the carbon analogue and allylic amide **26**, we were unable to use the oxazolidinone/NOE approach to prove the relative stereochemistry. However, comparison of the ^{1}H NMR spectra of all the allylic amides in this study clearly shows that certain signals (1-H_2, 2-H and 5-H_3) are particularly distinct for diastereomers **a** and **b**. Thus, careful inspection of the ^{1}H NMR spectra produced from rearrangement of the carbon analogue and allylic amide **10** allowed confirmation of diastereomer **b** as the major product from these reactions.
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