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Stereoselective β-hydroxy-α-amino acid synthesis *via* an ether-directed, palladium-catalysed aza-Claisen rearrangement

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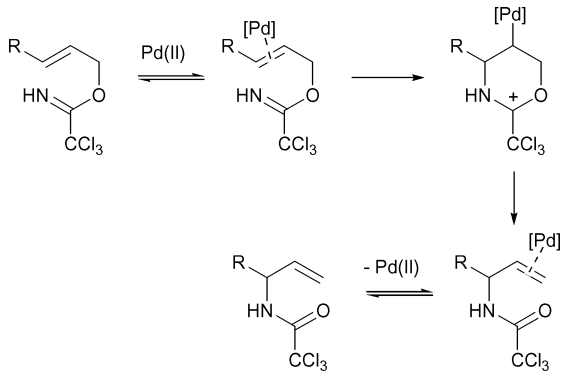
A highly diastereoselective synthesis of (2*S*,3*S*)-β-hydroxy-α-amino acids has been developed from enantiopure α-hydroxy acids using a MOM-ether-directed, palladium(II)-catalysed, aza-Claisen rearrangement of allylic acetimidates to effect the key step. This highly stereoselective process gave allylic amides in diastereomeric ratios of up to 14 : 1. Problems associated with the isolation of 1,3-products (anti-Claisen) from sterically demanding substrates *via* an *in situ* palladium(0)-catalysed rearrangement process were overcome by the addition of a re-oxidant, *p*-benzoquinone, leading to cleaner reactions and improved yields of the 3,3-products (Claisen). The target β-hydroxy-α-amino acids are an important class of natural products that are also components of more complex organic compounds with significant biological properties.

Introduction

Thermally promoted [3,3]-sigmatropic rearrangements of allylic imidates to allylic amides has found widespread application in organic chemistry due to the ease of transformation of readily available allylic alcohols under mild conditions to less available allylic amines and derivatives.[1] The reaction pathway for this transformation proceeds *via* a highly ordered chair-like transition state allowing excellent transfer of chirality to the final product.[1b] This conservation of stereochemistry has led to the use of the reaction for the asymmetric synthesis of a number of natural products.[2]

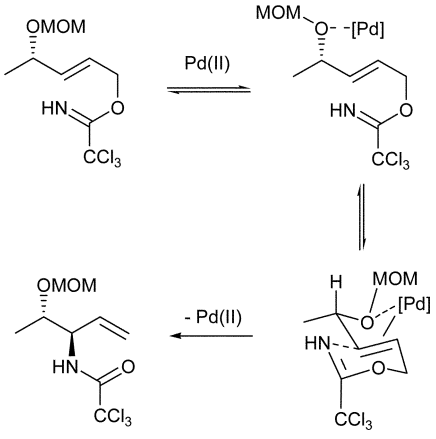
The metal-catalysed version of this reaction (aza-Claisen) first reported by Overman[1] using Hg(II) salts and then by Ikariya[3] using Pd(II) salts can be carried out at room temperature, giving the desired allylic amides cleanly in high yields. The reaction pathway for the palladium(II)-catalysed aza-Claisen reaction has been shown to follow a cyclisation-induced rearrangement mechanism involving intramolecular aminopalladation of the alkene followed by reductive elimination to generate the amide products (Scheme 1).[4]



Scheme 1 Pd(II)-catalysed rearrangement of allylic imidates *via* a cyclisation-induced mechanism.

Work on the development of asymmetric metal-catalysed aza-Claisen rearrangements has focused on the preparation of chiral Pd(II) catalysts.[5] While many of these catalysts are complex in structure, Overman and co-workers have recently reported a modified, monomeric cobalt oxazoline palladacycle which can catalyse the rearrangement of allylic trichloroacetimidates in good yield and with high asymmetric induction.[6]

We have made our own contribution to this field, utilising a substrate-directed aza-Claisen rearrangement for the stereoselective synthesis of allylic amides.[7] Substrate-directed reactions involve the pre-association of reagents with chiral functional groups in the vicinity of the reacting centre resulting in a stereoselective process.[8] Using a series of allylic trichloroacetimidates with various ether groups, it was shown that the methoxymethyl (MOM) ether is the most effective at directing the facial coordination of the palladium(II) catalyst, yielding the major stereoisomer in 82% de (Scheme 2).[7] Further evidence for this directing effect was achieved by the rearrangement of a carbon analogue of the MOM ether substrate, which produced the corresponding amide in only 33% de. Following on from this work, we decided to explore the versatility of this MOM-ether-directing effect for the general preparation of chiral allylic amides and to utilise these compounds for the stereoselective synthesis of biologically important β-hydroxy-α-amino acids.[9] We now describe this work in full, as well as the unexpected isolation of 1,3-products (anti-Claisen) from these rearrangements *via* a Pd(0)-catalysed allylic substitution reaction.



Scheme 2 Stereoselective MOM-ether-directed aza-Claisen rearrangement.

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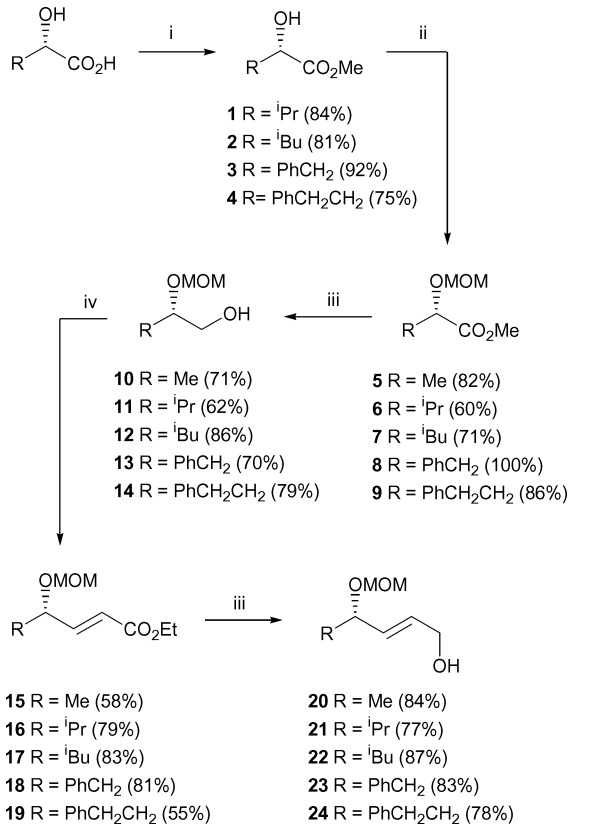
Results and discussion

Our initial aim in this project was the development of a flexible, efficient route for the synthesis of a series of *E*-allylic alcohols (Scheme 3). Commercially available α-hydroxy acids[10] were converted to MOM-protected α-hydroxy esters **5–9** by esterification using hydrochloric acid and methanol followed by reaction with bromomethyl methyl ether and Hünig's base. In previous work we have found it difficult to handle certain 2-methoxymethoxy aldehydes due to the volatility and easy decomposition of these compounds.[7] Therefore, the MOM-protected α-hydroxy esters **5–9** were reduced directly to the corresponding alcohols **10–14** using DIBAL-H.[7] These were converted to *E*-allylic esters **15–19** in good yields using a one-pot, Swern oxidation/Horner–Wadsworth–Emmons (HWE) reaction, thereby avoiding isolation of the volatile and unstable aldehyde intermediates.[11] Finally, reduction, again using DIBAL-H, gave the desired *E*-allylic alcohols **20–24**.



Scheme 3 *Reagents and conditions*: i. conc. HCl, MeOH, toluene, Δ; ii. MOMBr, EtN(iPr)$_2$, CH_2Cl_2, Δ; iii. DIBAL-H (2.2 equiv.), Et_2O, −78 °C to RT; iv. DMSO, $(COCl)_2$, NEt_3, CH_2Cl_2, −78 °C to RT, then triethyl phosphonoacetate, LiCl, DBU, MeCN.

Treatment of *E*-allylic alcohols **20–24** with DBU and trichloroacetonitrile provided *E*-allylic trichloroacetimidates **25–29**,[12] the substrates required for the directed aza-Claisen rearrangement (Scheme 4). This transformation can be carried out using sodium hydride as a base.[13] However, in our hands, the use of DBU is more reliable, giving the allylic trichloroacetimidates in higher yields. Allylic trichloroacetimidates are known to be relatively unstable[14] and thus, the work-up and purification of these compounds involves simply washing the reaction mixture through a small dry flash column of silica gel followed by removal of the solvent *in vacuo*.

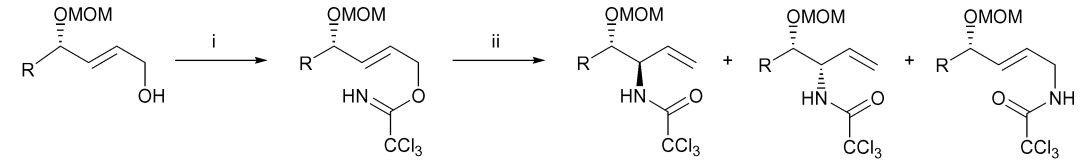
Table 1 Aza-Claisen rearrangement of *E*-allylic trichloroacetimidates **25–29**

Entry	R	Yield[a]	Ratio[b] (**a** : **b** : **c**)
1	Me (**30**)	64%	10 : 1 : 0
2	iPr (**31**)	58%	0 : 1 : 2
3	iBu (**32**)	60%	14 : 1 : 1
4	$PhCH_2$ (**33**)	54%	12 : 1 : 0
5	$PhCH_2CH_2$ (**34**)	65%	9 : 1 : 4

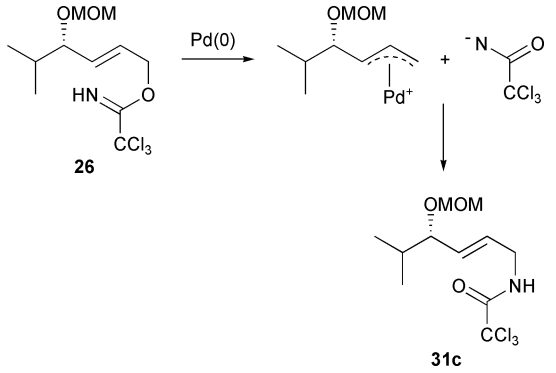
[a] Isolated combined yields of **a**, **b** and **c** from *E*-allylic alcohol. [b] Ratio in crude reaction mixture.

The aza-Claisen rearrangement of *E*-allylic trichloroacetimidates **25–29** was carried out at room temperature using bis(acetonitrile)palladium(II) chloride as the catalyst (Scheme 4, Table 1). As previously reported, rearrangement of substrate **25** (R = Me) is essentially complete after 4 hours to give an excellent 10 : 1 ratio of diastereomers **30a** and **30b** (3,3-Claisen products) in 64% yield.[7] Surprisingly, similar treatment of substrate **26** (R = iPr) with the Pd(II) catalyst required 48 hours for completion of the reaction and yielded none of the usual (3*R*,4*S*)-diastereomer **31a**. Instead, the major products from this reaction are the (3*S*,4*S*)-diastereomer **31b** and the 1,3-product (anti-Claisen) **31c** in a 1 : 2 ratio. The groups of Ikariya and Bosnich have investigated the metal-catalysed rearrangement of allylic imidates using both Pd(II) and Pd(0) complexes.[3,4b] These studies clearly demonstrated that the use of Pd(II) gives exclusively the 3,3-product (Claisen) while Pd(0), *via* a non-concerted ionisation pathway, produces predominantly the 1,3-product (anti-Claisen). Overman and co-workers have also reported the isolation of 1,3-products *via* an ionisation pathway.[5c,15] MOM-ether-directed rearrangement of substrate **26** is obviously suppressed by the combined steric bulk of the isopropyl group and the MOM ether. This steric hindrance also slows the formation of the other products, including the (3*S*,4*S*)-diastereomer **31b**, which is produced by direct coordination of the Pd(II) catalyst to the least hindered face of the alkene, followed by a concerted, cyclisation-induced rearrangement mechanism to give this specific stereoisomer.[7] Based on the work of Ikariya and Bosnich described above,[3,4b] it is proposed that 1,3-product **31c** is formed *via* a Pd(0)-catalysed allylic substitution reaction (Scheme 5) and that the Pd(0) likely arises by a competing β-elimination process during the slow Pd(II)-catalysed rearrangement of allylic imidate **26**.

Fortunately, treatment of allylic imidates **27–29** with the Pd(II) catalyst gave the desired (3*R*,4*S*)-diastereomers **32–34a** in good yield and excellent stereoselectivity (up to 14 : 1) (Table 1). The sterically encumbered tertiary centres contained within the side chains of these substrates are now further away from the reacting sp^2 centre of the alkene, allowing the MOM-ether-directed



Scheme 4 *Reagents and conditions*: i. Cl_3CCN, DBU, CH_2Cl_2, 0 °C to RT; ii. $PdCl_2(MeCN)_2$, THF, RT.



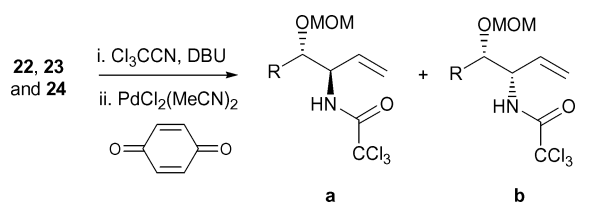
Scheme 5 Pd(0)-catalysed formation of 1,3-products (anti-Claisen).

process to take effect. Nevertheless, significant amounts of the 1,3-products were still isolated from these reactions, resulting in slightly lower than expected yields for the 3,3-products. Thus, while these substrates are able to undergo the MOM-ether-directed rearrangement, the reactions are still slow enough to produce trace amounts of Pd(0), which catalyses formation of the 1,3-products.

In an effort to optimise the yield of the 3,3-products and also provide evidence for the Pd(0)-catalysed formation of the 1,3-products, a suitably mild reagent was sought which could rapidly re-oxidise Pd(0) back to Pd(II). *p*-Benzoquinone is widely used for such a purpose in the Pd(II)-catalysed oxidation of alkenes.[16,17] Therefore, we were gratified to note that treatment of allylic imidates **27–29** with the Pd(II) catalyst and 2 equivalents of *p*-benzoquinone gave only the 3,3-products with improved yields from the corresponding allylic alcohol and again, in excellent stereoselectivity (Table 2). These experiments clearly demonstrate both the presence of Pd(0) during the Pd(II)-catalysed aza-Claisen rearrangement of allylic imidates **27–29** and also the effective suppression of this competing Pd(0)-catalysed pathway using *p*-benzoquinone as a re-oxidant.

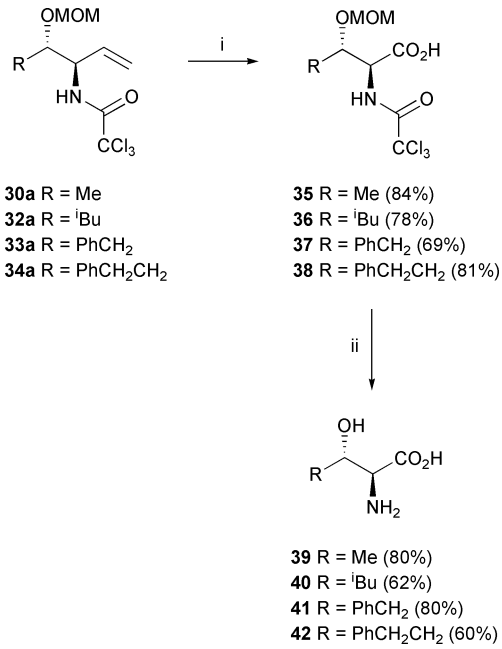
The (3*R*,4*S*)-allylic amides produced using the MOM-ether-directed aza-Claisen rearrangement were then converted to the corresponding (2*S*,3*S*)-β-hydroxy-α-amino acids (Scheme 6). Oxidation of the allylic amides was carried out according to the Sharpless protocol using catalytic ruthenium(III) trichloride hydrate and sodium metaperiodate.[18] Deprotection of the resulting carboxylic acids **35–38** under acidic conditions followed by purification with ion exchange chromatography gave the target compounds in good yields. Spectroscopic data for the (2*S*,3*S*)-β-hydroxy-α-amino acids were entirely consistent with literature reports,[19,20] thereby confirming our previous stereochemical assignment of the rearrangement products using oxazolidin-2-one derivatives and NOE experiments.[7]

Table 2 Treatment of allylic imidates **27–29** with the Pd(II) catalyst and *p*-benzoquinone



Entry	R	Yield[a]	Ratio[b] (**a** : **b**)
1	^{i}Bu (**32**)	73%	14 : 1
2	$PhCH_2$ (**33**)	70%	12 : 1
3	$PhCH_2CH_2$ (**34**)	69%	9 : 1

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



Scheme 6 *Reagents and conditions*: i. $RuCl_3 \cdot xH_2O$, $NaIO_4$, H_2O, CCl_4, MeCN; ii. 6 M HCl, Δ.

In summary, we have developed a novel approach for the diastereoselective synthesis of β-hydroxy-α-amino acids from enantiopure α-hydroxy acids. These target compounds are an important class of natural products that are also components of more complex organic compounds with interesting biological properties.[9] While the key step, the MOM-ether-directed palladium-catalysed aza-Claisen rearrangement does provide the desired 3,3-products in good yields and excellent diastereoselectivity, 1,3-products were also isolated *via* a competing Pd(0) pathway. However, this pathway was effectively inhibited using *p*-benzoquinone as an oxidant of Pd(0), resulting in the isolation of only the 3,3-products in greater yields and again with excellent stereoselectivity. Catalytic ruthenium oxidation of the resulting allylic amides and deprotection under acid conditions completed the synthesis of the β-hydroxy-α-amino acids.

Experimental

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 $KMnO_4$. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker DPX 400 spectrometer with chemical shift values in ppm 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 ($\lambda = 589$ nm) using a AA series Automatic polarimeter. $[\alpha]_D$ values are given in units 10^{-1} deg cm^2 g^{-1}.

Esterification of α-hydroxy acids

The α-hydroxy acid (5 mmol) was dissolved in toluene (40 mL) and methanol (25 mL). Concentrated hydrochloric acid (1 mL) was added and the reaction mixture was heated under reflux overnight. The reaction mixture was cooled to room temperature

and concentrated *in vacuo*. The resulting residue was neutralised with saturated sodium hydrogen carbonate solution (50 mL) and extracted with ethyl acetate (3 × 50 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated. Purification by Kugelrohr distillation gave the α-hydroxy esters as colourless oils. Hydroxy ester **3** became a white solid on standing.

Methyl (2*S*)-2-hydroxy-3-methylbutanoate (1). 84% yield; $[\alpha]_D^{21}$ +24.3 (*c* 1.0, $CHCl_3$); lit.[21] $[\alpha]_D^{25}$ +23.1 (*c* 2.5, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.87 (3H, d, *J* 6.8 Hz, 3-CH_3), 1.03 (3H, d, *J* 6.8 Hz, 4-H_3), 2.02 (1H, sept of d, *J* 6.8, 3.6 Hz, 3-H), 2.66 (1H, d, *J* 6.4 Hz, OH), 3.80 (3H, s, CO_2Me), 4.05 (1H, dd, *J* 6.4, 3.6 Hz, 2-H); δ_C (100 MHz, $CDCl_3$) 16.0 (CH_3), 18.8 (CH_3), 32.2 (CH), 52.4 (CH_3), 75.0 (CH), 175.4 (C); *m*/*z* (CI) 133.0872 (MH^+. $C_6H_{13}O_3$ requires 133.0865), 105 (8%) and 73 (7).

Methyl (2*S*)-2-hydroxy-4-methylpentanoate (2). 81% yield; $[\alpha]_D^{20}$ +3.9 (*c* 1.0, $CHCl_3$); lit.[21] $[\alpha]_D^{25}$ +2.2 (*c* 2.2, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.95 (3H, d, *J* 6.8 Hz, 5-H_3), 0.94 (3H, d, *J* 6.8 Hz, 4-CH_3), 1.54–1.60 (2H, m, 3-H_2), 1.83 (1H, m, 4-H), 2.63 (1H, d, *J* 6.0 Hz, OH), 3.79 (3H, s, CO_2Me), 4.19 (1H, dt, *J* 7.6, 6.0 Hz, 2-H); δ_C (100 MHz, $CDCl_3$) 21.6 (CH_3), 23.3 (CH), 24.4 (CH_3), 43.5 (CH_2), 52.5 (CH_3), 69.1 (CH), 176.4 (C); *m*/*z* (CI) 147.1023 (MH^+. $C_7H_{15}O_3$ requires 147.1021), 143 (8%) and 119 (11).

Methyl (2*S*)-2-hydroxy-3-phenylpropanoate (3). 92% yield; $[\alpha]_D^{21}$ −5.9 (*c* 1.0, $CHCl_3$); lit.[22] $[\alpha]_D^{20}$ −7.3 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.74 (1H, br s, OH), 3.00 (1H, dd, *J* 14.0, 6.8 Hz, 3-*H*H), 3.17 (1H, dd, *J* 14.0, 4.4 Hz, 3-H*H*), 3.81 (3H, s, CO_2Me), 4.49 (1H, dd, *J* 4.4, 2.4 Hz, 2-H), 7.23–7.36 (5H, m, Ph); δ_C (100 MHz, $CDCl_3$) 40.6 (CH_2), 52.5 (CH_3), 71.3 (CH), 126.9 (CH), 128.5 (CH), 129.5 (CH), 136.3 (CH), 174.6 (C); *m*/*z* (EI) 180.0786 (M^+. $C_{10}H_{12}O_3$ requires 180.0786), 162 (34%), 150 (7), 121 (16) and 91 (100).

Methyl (2*S*)-2-hydroxy-4-phenylbutanoate (4). 75% yield; $[\alpha]_D^{19}$ +23.7 (*c* 1.0, $CHCl_3$); lit.[23] $[\alpha]_D^{25}$ +30.9 (*c* 2.1, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.94–2.04 (1H, m, 3-*H*H), 2.11–2.21 (1H, m, 3-H*H*), 2.76–2.81 (2H, m, 4-H_2), 2.84 (1H, d, *J* 5.6 Hz, OH), 3.79 (1H, s, CO_2Me), 4.20 (1H, ddd, *J* 9.2, 5.6, 4.4 Hz, 2-H), 7.21–7.35 (5H, m, Ph); *m*/*z* (EI) 194.0941 (M^+. $C_{11}H_{14}O_3$ requires 194.0943), 176 (8%), 117 (20), 105 (58) and 90 (100).

Preparation of methoxymethyl ethers (5–9)

N,*N*-Diisopropylethylamine (1.5 equiv.) and bromomethyl methyl ether (1.5 equiv.) were added to a solution of the α-hydroxy ester (5 mmol) in dichloromethane (20 mL). The reaction mixture was then heated under reflux for 12 h before being diluted with dichloromethane (50 mL) and washed with 2 M hydrochloric acid solution (25 mL). The organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. Purification was carried out by flash column chromatography using diethyl ether–petroleum ether to give the desired compounds as colourless oils.

Ethyl (2*S*)-2-methoxymethoxypropanoate (5). 82% yield; $[\alpha]_D^{20}$ −92.3 (*c* 1.0, $CHCl_3$); lit.[24] $[\alpha]_D^{22}$ −88.1 (*c* 2.9, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.29 (3H, t, *J* 7.0, OCH_2CH_3), 1.43 (3H, d, *J* 7.0, 3-H_3), 3.39 (3H, s, OMe), 4.21 (2H, q, *J* 7.0, OCH_2CH_3), 4.24 (1H, q, *J* 7.0, 2-H), 4.69 (1H, d, *J* 7.0, OC*H*HO), 4.72 (1H, d, *J* 7.0, OCH*H*O); δ_C (100 MHz, $CDCl_3$) 14.9 (CH_3), 18.5 (CH_3), 55.9 (CH_3), 60.9 (CH_2), 71.5 (CH), 95.9 (CH_2), 173.1 (C); *m*/*z* (CI) 163.0969 (MH^+. $C_7H_{15}O_4$ requires 163.0970), 131 (100%) and 119 (5).

Methyl (2*S*)-2-methoxymethoxy-3-methylbutanoate (6). 60% yield; ν_{max}/cm^{-1} (neat) 2965 (CH), 1748 (CO), 1201, 1152, 1041, 916; $[\alpha]_D^{20}$ −76.0 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.97 (3H, d, *J* 6.8 Hz, 3-CH_3), 0.99 (3H, d, *J* 6.8 Hz, 4-H_3), 2.04–2.15 (1H, m, 3-H), 3.39 (3H, s, OMe), 3.75 (3H, s, CO_2Me), 3.89 (1H, d, *J* 5.6 Hz, 2-H), 4.66 (1H, d, *J* 7.2 Hz, OC*H*HO), 4.68 (1H, d, *J* 7.2 Hz, OCH*H*O); δ_C (100 MHz, $CDCl_3$) 17.7 (CH_3), 18.8 (CH_3), 31.5 (CH), 51.7 (CH_3), 56.1 (CH_3), 80.7 (CH), 96.5 (CH_2), 172.9 (C); *m*/*z* (CI) 177.1126 (MH^+. $C_8H_{17}O_4$ requires 177.1127), 145 (100%), 117 (34) and 79 (38).

Methyl (2*S*)-2-methoxymethoxy-4-methylpentanoate (7). 71% yield; ν_{max}/cm^{-1} (neat) 2956 (CH), 1750 (CO), 1203, 1158, 1026, 917; $[\alpha]_D^{20}$ −66.0 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.95 (3H, d, *J* 6.4 Hz, 5-H_3), 0.96 (3H, d, *J* 6.4 Hz, 4-CH_3), 1.50–1.57 (1H, m, 3-*H*H), 1.67–1.76 (1H, m, 3-H*H*), 1.78–1.87 (1H, m, 4-H), 3.40 (3H, s, OMe), 3.75 (3H, s, CO_2Me), 4.16 (1H, dd, *J* 9.2, 4.4 Hz, 2-H), 4.66 (1H, d, *J* 6.8 Hz, OC*H*HO), 4.69 (1H, d, *J* 6.8 Hz, OCH*H*O); δ_C (100 MHz, $CDCl_3$) 21.5 (CH_3), 23.2 (CH), 24.4 (CH_3), 41.8 (CH_2), 51.9 (CH_3), 56.1 (CH_3), 74.3 (CH), 96.4 (CH_2), 173.7 (C); *m*/*z* (CI) 191.1289 (MH^+. $C_9H_{19}O_4$ requires 191.1283) and 159 (100%).

Methyl (2*S*)-2-methoxymethoxy-3-phenylpropanoate (8). 100% yield; $[\alpha]_D^{21}$ −56.6 (*c* 1.0, $CHCl_3$); lit.[25] (opposite enantiomer) $[\alpha]_D$ +55.7 (*c* 0.8, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 3.01 (1H, dd, *J* 14.0, 9.2 Hz, 3-*H*H), 3.09 (3H, s, OMe), 3.13 (1H, dd, *J* 14.0, 4.4 Hz, 3-H*H*), 3.76 (3H, s, CO_2Me), 4.37 (1H, dd, *J* 9.2, 4.4 Hz, 2-H), 4.54 (1H, d, *J* 6.8 Hz, OC*H*HO), 4.66 (1H, d, *J* 6.8 Hz, OCH*H*O), 7.24–7.37 (5H, m, Ph); δ_C (100 MHz, $CDCl_3$) 39.2 (CH_2), 52.1 (CH_3), 55.7 (CH_3), 76.3 (CH), 96.0 (CH_2), 126.8 (CH), 128.4 (CH), 129.5 (CH), 137.0 (C), 172.6 (C); *m*/*z* (CI) 225.1124 (MH^+. $C_{12}H_{17}O_4$ requires 225.1127), 193 (100%), 162 (12), 133 (39) and 85 (22).

Methyl (2*S*)-2-methoxymethoxy-4-phenylbutanoate (9). 86% yield; ν_{max}/cm^{-1} (neat) 2949 (CH), 1749 (CO), 1655 (C=C), 1644, 1028; $[\alpha]_D^{18}$ −28.6 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.10 (2H, td, *J* 8.4, 6.4 Hz, 3-H_2), 2.68–2.84 (2H, m, 4-H_2), 3.42 (3H, s, OMe), 3.74 (3H, s, CO_2Me), 4.15 (1H, t, *J* 6.4 Hz, 2-H), 4.68 (1H, d, *J* 6.8 Hz, OC*H*HO), 4.72 (1H, d, *J* 6.8 Hz, OCH*H*O), 7.18–7.31 (5H, m, Ph); δ_C (100 MHz, $CDCl_3$) 31.4 (CH_2), 34.5 (CH_2), 52.0 (CH_3), 56.2 (CH), 75.1 (CH_3), 96.5 (CH_2), 126.1 (CH), 128.5 (CH), 128.5 (CH), 141.0 (C), 173.1 (C); *m*/*z* (CI) 207.1015 ($MH^+ - CH_3OH$. $C_{12}H_{15}O_3$ requires 207.1021), 189 (89), 147 (52) and 105 (23).

DIBAL-H reduction to alcohols 10–14

The ester (5 mmol) was dissolved in diethyl ether (30 mL) and cooled to −78 °C. DIBAL-H (1 M in hexane) (2.2 equiv.) 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 (20 mL) and being warmed to room temperature, producing a white precipitate. The reaction mixture 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 by flash column chromatography using diethyl ether–petroleum gave the desired compounds as colourless oils.

(2*S*)-2-Methoxymethoxypropan-1-ol (10). 71% yield; ν_{max}/cm^{-1} (neat) 3409 (OH), 2930 (CH), 1454, 1377, 1141, 1101, 1025; $[\alpha]_D^{25}$ −80.0 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.18 (3H, d, *J* 6.4 Hz, 3-H_3), 2.60 (1H, br s, OH), 3.43 (3H, s, OMe), 3.46 (1H, dd, *J* 11.8, 7.3 Hz, 1-*H*H), 3.57 (1H, dd, *J* 11.8, 2.8 Hz, 1-H*H*), 3.70 (1H, m, 2-H), 4.71 (1H, d, *J* 6.9 Hz, OC*H*HO), 4.76 (1H, d, *J* 6.9 Hz, OCH*H*O); δ_C (100 MHz, $CDCl_3$) 17.4 (CH_3), 55.9 (CH_3), 67.4 (CH_2), 77.3 (CH), 96.5 (CH_2); *m*/*z* (CI) 121.0866 (MH^+. $C_5H_{13}O_3$ requires 121.0865), 119 (8%), 89 (100) and 87 (19).

(2*S*)-2-Methoxymethoxy-3-methylbutan-1-ol (11). 62% yield; ν_{max}/cm^{-1} (neat) 3423 (OH), 2957 (CH), 1152, 1095, 1027, 916; $[\alpha]_D^{19}$ +80.3 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.94 (3H, d, *J* 6.8 Hz, 3-CH_3), 0.95 (3H, d, *J* 6.8 Hz, 4-H_3), 1.78–1.90 (1H, m, 3-H), 3.17 (1H, dd, *J* 9.2, 3.2 Hz, OH), 3.29 (1H, m, 2-H), 3.45 (3H, s, OMe), 3.61 (1H, m, 1-*H*H), 3.61 (1H, ddd, *J*

12.0, 9.2, 2.4 Hz, 1-H*H*), 4.66 (1H, d, *J* 6.8 Hz, OC*H*HO), 4.76 (1H, d, *J* 6.8 Hz, OCH*H*O); δ_C (100 MHz, $CDCl_3$) 18.2 (CH_3), 18.9 (CH_3), 30.3 (CH), 55.7 (CH_3), 63.9 (CH_2), 88.2 (CH), 97.8 (CH_2); *m*/*z* (CI) 149.1174 (MH^+. $C_7H_{17}O_3$ requires 149.1178), 117 (100%), 87 (20) and 71 (18).

(2*S*)-Methoxymethoxy-4-methylpentan-1-ol (12). 86% yield; ν_{max}/cm^{-1} (neat) 3402 (OH), 2951 (CH), 1469, 1099, 1029, 917; $[\alpha]_D^{19}$ +57.1 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.90 (3H, d, *J* 6.8 Hz, 5-H_3), 0.92 (3H, d, *J* 6.8 Hz, 4-CH_3), 1.20 (1H, ddd, *J* 14.0, 8.4, 5.2 Hz, 3-*H*H), 1.47 (1H, ddd, *J* 14.0, 8.4, 5.6 Hz, 3-H*H*), 1.68–1.77 (1H, m, 4-H), 3.26 (1H, dd, *J* 9.2, 3.6 Hz, OH), 3.44 (3H, s, OMe), 3.47 (1H, m, 2-H), 3.55–3.65 (2H, m, 1-H_2), 4.68 (1H, d, *J* 6.8 Hz, OC*H*HO), 4.73 (1H, d, *J* 6.8 Hz, OCH*H*O); δ_C (100 MHz, $CDCl_3$) 22.2 (CH_3), 23.2 (CH), 24.4 (CH_3), 40.7 (CH_2), 55.7 (CH_3), 66.2 (CH_2), 81.0 (CH), 97.1 (CH_2); *m*/*z* (CI) 163.1333 (MH^+. $C_8H_{19}O_3$ requires 163.1334), 131 (100%), 101 (29), 83 (21).

(2*S*)-2-Methoxymethoxy-3-phenylpropan-1-ol (13). 70% yield; ν_{max}/cm^{-1} (neat) 3386 (OH), 2930 (CH), 1495, 1454, 1146, 1104, 1029, 913, 699; $[\alpha]_D^{21}$ +20.7 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.79–2.94 (3H, m, 3-H_2 and OH), 3.37 (3H, s, OMe), 3.55 (1H, m, 1-*H*H), 3.67 (1H, m, 1-H*H*), 3.87 (1H, m, 2-H), 4.59 (1H, d, *J* 7.2 Hz, OC*H*HO), 4.70 (1H, d, *J* 7.2 Hz, OCH*H*O), 7.24–7.38 (5H, m, Ph); δ_C (100 MHz, $CDCl_3$) 38.2 (CH_2), 55.6 (CH_3), 64.9 (CH_2), 82.1 (CH), 96.7 (CH_2), 126.4 (CH), 128.4 (CH), 129.4 (CH), 138.0 (C); *m*/*z* (CI) 197.1179 (MH^+. $C_{11}H_{17}O_3$ requires 197.1178), 165 (76%), 147 (100), 136 (12), 117 (15) and 105 (12).

(2*S*)-2-Methoxymethoxy-4-phenylbutan-1-ol (14). 79% yield; ν_{max}/cm^{-1} (neat) 3421 (OH), 2934 (CH), 1146, 1101, 1024, 916; $[\alpha]_D^{18}$ +47.5 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.78–1.94 (2H, m, 3-H_2), 2.68 (1H, ddd, *J* 14.0, 9.6, 7.2 Hz, 4-*H*H), 2.80 (1H, ddd, *J* 14.0, 9.6, 5.6 Hz, 4-H*H*), 3.48 (3H, s, OMe), 3.54–3.65 (3H, m, 2-H and 1-H_2), 4.70 (1H, d, *J* 6.8 Hz, OC*H*HO), 4.80 (1H, d, *J* 6.8 Hz, OCH*H*O), 7.20–7.35 (5H, m, Ph); δ_C (100 MHz, $CDCl_3$) 31.7 (CH_2), 33.3 (CH_2), 55.8 (CH_3), 65.8 (CH_2), 81.9 (CH), 97.2 (CH_2), 126.0 (CH), 128.4 (CH), 128.5 (CH), 141.7 (C); *m*/*z* (CI) 211 (MH^+, 7%), 179 (92), 161 (100), 131 (55) and 105 (17); (Found: C, 68.4; H, 8.6. $C_{12}H_{18}O_3$ requires C, 68.5; H, 8.6%).

Synthesis of allylic esters 15–19 using the one-pot Swern/Horner–Wadsworth–Emmons reaction

Methyl sulfoxide (2.4 equiv.) was added to a stirred solution of oxalyl chloride (1.2 equiv.) in dichloromethane (20 mL) at −78 °C. This mixture was stirred for 0.25 h before the alcohol (5 mmol) in dichloromethane (30 mL) was added. The mixture was stirred for a further 0.25 h before triethylamine (5 equiv.) was added. This reaction mixture was then allowed to stir for 2 h. In a second flask, a solution of lithium chloride (1.5 equiv.), triethyl phosphonoacetate (1.5 equiv.) and 1,8-diazabicyclo[5.4.0]undec-7-ene (1.5 equiv.) 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 (50 mL) and then concentrated *in vacuo*. 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 liquid. Purification was carried out by flash column chromatography using diethyl ether–petroleum ether to give the desired compounds as colourless oils.

Ethyl (2*E*,4*S*)-4-methoxymethoxypent-2-enoate (15). 58% yield for two steps; ν_{max}/cm^{-1} (neat) 2981 (CH), 1720 (CO), 1660 (C=C), 1271, 1032; $[\alpha]_D^{21}$ −80.0 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.30 (6H, m, OCH_2CH_3 and 5-H_3), 3.37 (3H, s, OMe), 4.20 (2H, q, *J* 7.1 Hz, OCH_2CH_3), 4.35 (1H, quin of d, *J* 6.6, 1.3 Hz, 4-H), 4.62 (2H, s, OCH_2O), 5.99 (1H, dd, *J* 15.7, 2.1 Hz, 2-H), 6.87 (1H, dd, *J* 15.7, 6.3 Hz, 3-H); δ_C (100 MHz, $CDCl_3$) 14.6 (CH_3), 20.9 (CH_3), 55.8 (CH_3), 60.8 (CH_2), 71.4 (CH), 94.8 (CH_2), 121.4 (CH), 149.1 (CH), 166.7 (C); *m*/*z* (CI) 189.1125 (MH^+. $C_9H_{17}O_4$ requires 189.1127), 159 (39%), 143 (46), 127 (58) and 101 (12).

Ethyl (2*E*,4*S*)-4-methoxymethoxy-5-methylhex-2-enoate (16). 79% yield for two steps; ν_{max}/cm^{-1} (neat) 2965 (CH), 1718 (CO), 1656 (C=C), 1249, 1153, 1029, 986, 920; $[\alpha]_D^{19}$ −96.2 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.93 (3H, d, *J* 6.8 Hz, 5-CH_3), 0.98 (3H, d, *J* 6.8 Hz, 6-H_3), 1.31 (3H, t, *J* 7.2 Hz, OCH_2CH_3), 1.82–1.93 (1H, m, 5-H), 3.38 (3H, s, OMe), 3.95 (1H, m, 4-H), 4.18 (2H, q, *J* 7.2 Hz, OCH_2CH_3), 4.58 (1H, d, *J* 6.8 Hz, OC*H*HO), 4.63 (1H, d, *J* 6.8 Hz, OCH*H*O), 5.98 (1H, dd, *J* 15.6, 1.2 Hz, 2-H), 6.82 (1H, dd, *J* 15.6, 6.8 Hz, 3-H); δ_C (100 MHz, $CDCl_3$) 14.2 (CH_3), 18.2 (CH_3), 18.3 (CH_3), 32.6 (CH), 55.7 (CH_3), 60.5 (CH_2), 80.2 (CH), 94.7 (CH_2), 123.0 (CH), 146.5 (CH), 166.2 (C); *m*/*z* (CI) 217.1441 (MH^+. $C_{11}H_{21}O_4$ requires 217.1440), 187 (17%), 155 (100) and 127 (5).

Ethyl (2*E*,4*S*)-4-methoxymethoxy-6-methylhept-2-enoate (17). 83% yield over two steps; ν_{max}/cm^{-1} (neat) 2954 (CH), 1718 (CO), 1659 (C=C), 1266, 1161, 984, 919; $[\alpha]_D^{21}$ −125.6 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.94 (3H, d, *J* 6.4 Hz, 6-CH_3), 0.95 (3H, d, *J* 6.4 Hz, 7-H_3), 1.30 (3H, t, *J* 7.2 Hz, OCH_2CH_3), 1.34 (1H, m, 5-*H*H), 1.58 (1H, ddd, *J* 14.0, 8.4, 6.0 Hz, 5-H*H*), 1.73–1.84 (1H, m, 6-H), 3.39 (3H, s, OMe), 4.20 (2H, q, *J* 7.2 Hz, OCH_2CH_3), 4.27 (1H, m, 4-H), 4.57 (1H, d, *J* 6.8 Hz, OC*H*HO), 4.64 (1H, d, *J* 6.8 Hz, OCH*H*O), 5.97 (1H, dd, *J* 15.6, 1.2 Hz, 2-H), 6.81 (1H, dd, *J* 15.6, 6.8 Hz, 3-H); δ_C (100 MHz, $CDCl_3$) 14.3 (CH_3), 22.1 (CH_3), 23.1 (CH_3), 24.3 (CH), 44.2 (CH_2), 55.7 (CH_3), 60.5 (CH_2), 73.6 (CH), 94.6 (CH_2), 121.7 (CH), 148.2 (CH), 166.3 (C); *m*/*z* (CI) 231.1594 (MH^+. $C_{12}H_{23}O_4$ requires 231.1596), 201 (63%), 169 (100) and 129 (6).

Ethyl (2*E*,4*S*)-4-methoxymethoxy-5-phenylpent-2-enoate (18). 81% yield over two steps; ν_{max}/cm^{-1} (neat) 2925 (CH), 1716 (CO), 1268, 1149, 1016, 699; $[\alpha]_D^{21}$ −56.6 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.32 (3H, t, *J* 7.2 Hz, OCH_2CH_3), 2.92 (2H, d, *J* 6.8 Hz, 5-H_2), 3.08 (3H, s, OMe), 4.23 (2H, q, *J* 7.2 Hz, OCH_2CH_3), 4.43–4.49 (2H, m, 4-H and OC*H*HO), 4.61 (2H, d, *J* 6.8 Hz, OCH*H*O), 6.01 (1H, dd, *J* 15.6, 1.2 Hz, 2-H), 6.90 (1H, dd, *J* 15.6, 6.0 Hz, 3-H), 7.23–7.35 (5H, m, Ph); δ_C (100 MHz, $CDCl_3$) 14.3 (CH_3), 41.6 (CH_2), 55.4 (CH_3), 60.6 (CH_2), 75.9 (CH), 94.5 (CH_2), 122.1 (CH), 126.6 (CH), 128.4 (CH), 129.6 (CH), 137.4 (C), 147.1 (CH), 166.2 (C); *m*/*z* (EI) 264.1363 (M^+. $C_{15}H_{20}O_4$ requires 264.1362), 203 (2%), 173 (21), 136 (12), 129 (11), 85 (63) and 83 (100).

Ethyl (2*E*,4*S*)-4-methoxymethoxy-6-phenylhex-2-enoate (19). 55% yield over two steps; ν_{max}/cm^{-1} (neat) 2944 (CH), 1717 (CO), 1658 (C=C), 1265, 1147, 1020; $[\alpha]_D^{19}$ −52.0 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.31 (3H, t, *J* 7.2 Hz, OCH_2CH_3), 1.86–2.02 (2H, m, 5-H_2), 2.67–2.82 (2H, m, 6-H_2), 3.41 (3H, s, OMe), 4.21 (2H, q, *J* 7.2 Hz, OCH_2CH_3), 4.25 (1H, m, 4-H), 4.62 (1H, d, *J* 6.8 Hz, OC*H*HO), 4.67 (1H, d, *J* 6.8 Hz, OCH*H*O), 6.01 (1H, dd, *J* 15.6, 1.6 Hz, 2-H), 6.86 (1H, dd, *J* 15.6, 6.0 Hz, 3-H), 7.18–7.32 (5H, m, Ph); δ_C (100 MHz, $CDCl_3$) 14.3 (CH_3), 31.4 (CH_2), 36.6 (CH_2), 55.8 (CH_3), 60.6 (CH_2), 74.9 (CH), 94.8 (CH_2), 122.2 (CH), 126.0 (CH), 128.4 (CH), 128.5 (CH), 141.5 (C), 147.6 (CH), 166.2 (C); *m*/*z* 279 (MH^+, 52%), 247 (50), 217 (100), 216 (7) and 173 (6); (Found: C, 68.8; H, 8.0. $C_{16}H_{22}O_4$ requires C, 69.0; H, 8.0%).

DIBAL-H reduction to allylic alcohols 20–24

The allylic ester (4 mmol) was dissolved in diethyl ether (20 mL) and cooled to −78 °C. DIBAL-H (1 M in hexane) (2.2 equiv.) was added dropwise and the reaction mixture was allowed to stir at −78 °C for 2 h then overnight at room temperature. The reaction was cooled to 0 °C, quenched by the addition of a saturated solution of ammonium chloride

(20 mL) and warmed to room temperature. 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 using diethyl ether–petroleum ether to give the desired compounds as colourless oils.

(2*E*,4*S*)-4-Methoxymethoxypent-2-en-1-ol (20). 84% yield; ν_{max}/cm^{-1} (neat) 3404 (OH), 2931 (CH), 1446, 1373, 1217, 1026; $[\alpha]_D^{23}$ −117.9 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.27 (3H, d, *J* 6.4 Hz, 5-H_3), 2.21 (1H, br s, OH), 3.37 (3H, s, OMe), 4.14 (2H, dd, *J* 5.1, 1.6 Hz, 1-H_2), 4.16 (1H, quin, *J* 6.4 Hz, 4-H), 4.57 (1H, d, *J* 6.7 Hz, OC*H*HO), 4.66 (1H, d, *J* 6.7 Hz, OCH*H*O), 5.63 (1H, ddt, *J* 15.0, 7.0, 1.6 Hz, 3-H), 5.81 (1H, dt, *J* 15.0, 5.1 Hz, 2-H); δ_C (100 MHz, $CDCl_3$) 21.3 (CH_3), 55.3 (CH_3), 63.0 (CH_2), 72.0 (CH), 93.8 (CH_2), 130.9 (CH), 132.8 (CH); *m*/*z* (CI) 129.0910 ($MH^+ - H_2O$. $C_7H_{13}O_2$ requires 129.0916), 117 (63) and 85 (100%).

(2*E*,4*S*)-4-Methoxymethoxy-5-methylhex-2-en-1-ol (21). 77% yield; ν_{max}/cm^{-1} (neat) 3386 (OH), 2958 (CH), 1469, 1152, 1089, 1030, 973, 920; $[\alpha]_D^{20}$ −124.3 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.89 (3H, d, *J* 6.8 Hz, 5-CH_3), 0.96 (3H, d, *J* 6.8 Hz, 6-H_3), 1.71 (1H, sept, *J* 6.8 Hz, 5-H), 1.86 (1H, t, *J* 5.6 Hz, OH), 3.37 (3H, s, OMe), 3.73 (1H, br t, *J* 6.8 Hz, 4-H), 4.16 (2H, br t, *J* 5.6 Hz, 1-H_2), 4.51 (1H, d, *J* 6.8 Hz, OC*H*HO), 4.69 (1H, d, *J* 6.8 Hz, OCH*H*O), 5.54 (1H, ddt, *J* 15.6, 8.0, 1.6 Hz, 3-H), 5.79 (1H, dt, *J* 15.6, 5.6 Hz, 2-H); δ_C (100 MHz, $CDCl_3$) 18.5 (CH_3), 18.6 (CH_3), 32.7 (CH), 55.5 (CH_3), 62.9 (CH_2), 81.5 (CH), 93.7 (CH_2), 129.6 (CH), 133.3 (CH); *m*/*z* (CI) 145.1227 ($MH^+ - CH_2O$. $C_8H_{17}O_2$ requires 145.1229), 125 (8%), 113 (38), 95 (100) and 85 (110).

(2*E*,4*S*)-4-Methoxymethoxy-6-methylhept-2-en-1-ol (22). 87% yield; ν_{max}/cm^{-1} (neat) 3332 (OH), 2952 (CH), 1560, 1092, 1029, 971, 916; $[\alpha]_D^{19}$ −126.4 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.92 (3H, d, *J* 6.4 Hz, 6-CH_3), 0.94 (3H, d, *J* 6.4 Hz, 7-H_3), 1.29 (1H, m, 5-*H*H), 1.56 (1H, m, 5-H*H*), 1.69–1.81 (1H, m, 6-H), 3.38 (3H, s, OMe), 4.12 (1H, m, 4-H), 4.15 (2H, dt, *J* 5.2, 1.2 Hz, 1-H_2), 4.52 (1H, d, *J* 6.8 Hz, OC*H*HO), 4.71 (1H, d, *J* 6.8 Hz, OCH*H*O), 5.55 (1H, ddt, *J* 15.6, 8.0, 1.2 Hz, 3-H), 5.79 (1H, dt, *J* 15.6, 5.2 Hz, 2-H); δ_C (100 MHz, $CDCl_3$) 22.3 (CH_3), 23.0 (CH_3), 24.3 (CH), 44.8 (CH_2), 55.5 (CH_3), 63.0 (CH_2), 74.4 (CH), 93.6 (CH_2), 131.8 (CH), 131.9 (CH); *m*/*z* (CI) 144 ($MH^+ - CH_3OCH_2$, 4%), 127 (100), 109 (92) and 85 (42).

(2*E*,4*S*)-4-Methoxymethoxy-5-phenylpent-2-en-1-ol (23). 83% yield; ν_{max}/cm^{-1} (neat) 3370 (OH), 2888 (CH), 1635 (C=C), 1496, 1453, 1092, 1028; $[\alpha]_D^{21}$ −86.3 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.42 (1H, s, OH), 2.86 (1H, dd, *J* 13.6, 5.6 Hz, 5-*H*H), 2.92 (1H, dd, *J* 13.6, 8.0 Hz, 5-H*H*), 3.08 (3H, s, OMe), 4.17 (2H, m, 1-H_2), 4.31 (1H, m, 4-H), 4.46 (1H, d, *J* 6.8 Hz, OC*H*HO), 4.68 (1H, d, *J* 6.8 Hz, OCH*H*O), 5.67 (1H, ddt, *J* 15.6, 7.6, 1.2 Hz, 3-H), 5.83 (1H, dt, *J* 15.6, 5.2 Hz, 2-H), 7.18–7.36 (5H, m, Ph); δ_C (100 MHz, $CDCl_3$) 42.3 (CH_2), 55.2 (CH_3), 62.9 (CH_2), 76.8 (CH), 93.6 (CH_2), 126.3 (CH), 128.2 (CH), 129.7 (CH), 130.9 (CH), 132.3 (CH), 138.2 (C); *m*/*z* (CI) 205 ($MH^+ - H_2O$, 32%), 175 (21), 161 (69), 143 (100) and 129 (8).

(2*E*,4*S*)-4-Methoxymethoxy-6-phenylhex-2-en-1-ol (24). 78% yield; (Found: C, 71.0; H, 8.6. $C_{14}H_{20}O_3$ requires C, 71.2; H, 8.6%); ν_{max}/cm^{-1} (neat) 3408 (OH), 2927 (CH), 1603 (C=C), 1146, 1093, 1028, 972, 917, 699; $[\alpha]_D^{16}$ −93.7 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.41 (1H, br s, OH), 1.80–2.03 (2H, m, 5-H_2), 2.63–2.81 (2H, m, 6-H_2), 3.40 (3H, s, OMe), 4.09 (1H, q, *J* 7.2 Hz, 4-H), 4.17 (2H, dd, *J* 5.2, 1.6 Hz, 1-H_2), 4.57 (1H, d, *J* 6.8 Hz, OC*H*HO), 4.72 (1H, d, *J* 6.8 Hz, OCH*H*O), 5.61 (1H, ddt, *J* 15.6, 7.2, 1.6 Hz, 3-H), 5.84 (1H, dt, *J* 15.6, 5.2 Hz, 2-H), 7.17–7.32 (5H, m, Ph); δ_C (100 MHz, $CDCl_3$) 31.7 (CH_2), 37.2 (CH_2), 55.6 (CH_3), 62.9 (CH_2), 75.9 (CH), 93.9 (CH_2), 125.9 (CH), 128.4 (CH), 128.4 (CH), 131.2 (CH), 132.4 (CH), 142.0 (C); *m*/*z* (CI) 219 ($MH^+ - H_2O$, 12%), 199 (15), 175 (96), 157 (100) and 131 (86).

Allylic trichloroacetimidate synthesis and subsequent rearrangement with bis(acetonitrile)palladium(II) chloride

The allylic alcohol (2 mmol) was dissolved in dichloromethane (20 mL) and cooled to 0 °C. 1,8-Diazabicyclo[5.4.0]undec-7-ene (1.2 equiv.) and trichloroacetonitrile (1.5 equiv.) 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 dry silica plug and the filtrate was concentrated *in vacuo* to give an orange liquid. 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 24–48 h. Concentration *in vacuo* followed by purification by flash column chromatography eluting with diethyl ether–petroleum ether gave all products as colourless oils.

(3*R*,4*S*)-3-(Trichloromethylcarbonylamino)-4-(methoxymethoxy)penta-1-ene (30a). 64% yield; ν_{max}/cm^{-1} (neat) 3302 (NH), 2935 (CH), 1713 (CO), 1643 (C=C), 1511, 1148, 1028, 819; δ_H (400 MHz, $CDCl_3$) 1.27 (3H, d, *J* 6.4 Hz, 5-H_3), 3.44 (3H, s, OMe), 3.87 (1H, qd, *J* 6.4, 2.4 Hz, 4-H), 4.37 (1H, m, 3-H), 4.70 (1H, d, *J* 6.8, OC*H*HO), 4.73 (1H, d, *J* 6.8 Hz, OCH*H*O), 5.36 (2H, m, 1-H_2), 5.89 (1H, m, 2-H), 7.89 (1H, br s, NH); δ_C (100 MHz, $CDCl_3$) 18.4 (CH_3), 56.2 (CH_3), 58.1 (CH), 77.7 (CH), 92.1 (C), 97.0 (CH_2), 119.6 (CH_2), 131.8 (CH), 161.7 (C); *m*/*z* (CI) 290.0127 (MH^+. $C_9H_{15}O_3NCl_3$ requires 290.0118), 258 (76%), 246 (21), 214 (28), 196 (62) and 162 (29).

(3*S*,4*S*)-3-(Trichloromethylcarbonylamino)-4-(methoxymethoxy)-5-methylhexa-1-ene (31b) and (2*E*,4*S*)-1-(trichloromethylcarbonylamino)-4-(methoxymethoxy)-5-methylhexa-2-ene (31c). 58% combined yield; **31c**: ν_{max}/cm^{-1} (neat) 3422 (NH), 2853 (CH), 1655, 1037, 992, 793; $[\alpha]_D^{18}$ −89.7 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.90 (3H, d, *J* 6.8 Hz, 5-CH_3), 0.97 (3H, d, *J* 6.8 Hz, 6-H_3), 1.74–1.84 (1H, m, 5-H), 3.38 (3H, s, OMe), 3.76 (1H, t, *J* 6.8 Hz, 4-H), 4.08 (2H, d, *J* 6.8 Hz, 1-H_2), 4.53 (1H, d, *J* 6.8 Hz, OC*H*HO), 4.69 (1H, d, *J* 6.8 Hz, OCH*H*O), 5.64 (1H, dd, *J* 15.2, 6.8 Hz, 3-H), 5.79 (1H, m, 2-H); δ_C (100 MHz, $CDCl_3$) 17.3 (CH_3), 17.5 (CH_3), 31.6 (CH), 43.3 (CH_2), 54.5 (CH_3), 76.2 (C), 79.7 (CH), 92.9 (CH_2), 128.5 (CH), 132.3 (CH), 161.8 (C); *m*/*z* (CI) 276 ($MH^+ - CH_3OCH_2$, 11%), 240 (11), 204 (5) and 168 (6); **31b**: ν_{max}/cm^{-1} (neat) 3422 (NH), 2862 (CH), 1680, 1041, 995; $[\alpha]_D^{25}$ +61.8 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.98 (3H, d, *J* 6.8 Hz, 5-CH_3), 1.00 (3H, d, *J* 6.8 Hz, 6-H_3), 1.77–1.86 (1H, m, 5-H), 3.13 (1H, dd, *J* 10.0, 1.6 Hz, 4-H), 3.44 (3H, s, OMe), 4.56 (1H, m, 3-H), 4.62 (1H, d, *J* 6.4 Hz, OC*H*HO), 4.79 (1H, d, *J* 6.4 Hz, OCH*H*O), 5.31 (1H, d, *J* 10.0 Hz, 1-*H*H), 5.36 (1H, d, *J* 17.2 Hz, 1-H*H*), 5.80 (1H, ddd, *J* 17.2, 10.0, 6.8 Hz, 2-H), 8.49 (1H, br d, *J* 6.8 Hz, NH); δ_C (100 MHz, $CDCl_3$) 18.9 (CH_3), 19.6 (CH_3), 31.0 (CH), 54.7 (CH_3), 55.8 (CH), 90.9 (CH), 93.0 (C), 99.3 (CH_2), 118.8 (CH_2), 131.5 (CH), 161.5 (C); *m*/*z* (CI) 276 ($MH^+ - CH_3OCH_2$, 12%), 240 (5), 204 (3) and 168 (2).

(3*R*,4*S*)-3-(Trichloromethylcarbonylamino)-4-(methoxymethoxy)-6-methylhepta-1-ene (32a) and (2*E*,4*S*)-1-(trichloromethylcarbonylamino)-4-(methoxymethoxy)-6-methylhepta-2-ene (32c). 60% combined yield; **32c**: ν_{max}/cm^{-1} (neat) 2594 (CH), 1769 (CO), 1469, 1154, 1096, 1035; $[\alpha]_D^{20}$ −91.1 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.92 (3H, d, *J* 6.4 Hz, 6-CH_3), 0.93 (3H, d, *J* 6.4 Hz, 7-H_3), 1.25 (1H, ddd, *J* 13.6, 8.2, 5.6 Hz, 5-*H*H), 1.51 (1H, ddd, *J* 13.6, 8.2, 6.4 Hz, 5-H*H*), 1.70–1.81 (1H, m, 6-H), 3.37 (3H, s, OMe), 4.05 (2H, d, *J* 6.8 Hz, 1-H_2), 4.11 (1H, m, 4-H), 4.51 (1H, d, *J* 6.8 Hz, OC*H*HO), 4.68 (1H, d, *J* 6.8 Hz, OCH*H*O), 5.62 (1H, dd, *J* 15.2, 7.6 Hz, 3-H), 5.81 (1H, dt, *J* 15.2, 6.8 Hz, 2-H); δ_C (100 MHz, $CDCl_3$) 22.2 (CH_3), 23.0 (CH), 24.2 (CH_3), 44.3 (CH_2), 44.6 (CH_2), 55.5 (CH_3), 73.9 (CH), 93.8 (CH_2), 96.2 (C), 128.3 (CH), 135.2 (CH), 161.9 (C); *m*/*z* (CI)

288 ($MH^+ - CH_3OCH_2$, 32%), 279 (11), 254 (10) and 218 (7); **32a**; ν_{max}/cm^{-1} (neat) 3263 (NH), 2951 (CH), 1713 (CO), 1625 (C=C), 1517, 1032, 823, 680; $[\alpha]_D^{19}$ +37.0 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.90 (3H, d, *J* 6.4 Hz, 6-CH_3), 0.94 (3H, d, *J* 6.4 Hz, 7-H_3), 1.25 (1H, ddd, *J* 12.8, 9.2, 4.4 Hz, 5-*H*H), 1.53 (1H, ddd, *J* 12.8, 9.2, 5.6 Hz, 5-H*H*), 1.68–1.80 (1H, m, 6-H), 3.44 (3H, s, OMe), 3.66 (1H, ddd, *J* 9.2, 4.4, 1.6 Hz, 4-H), 4.37 (1H, m, 3-H), 4.66 (1H, d, *J* 6.8 Hz, OC*H*HO), 4.75 (1H, d, *J* 6.8 Hz, OCH*H*O), 5.31 (1H, d, *J* 1.6 Hz, 1-*H*H), 5.35 (1H, m, 1-H*H*), 5.78–5.91 (1H, m, 2-H), 8.36 (1H, br d, *J* 6.8 Hz, NH); δ_C (100 MHz, $CDCl_3$) 22.2 (CH_3), 23.2 (CH_3), 24.4 (CH), 42.0 (CH_2), 56.0 (CH), 56.9 (CH_3), 82.2 (CH), 93.0 (C), 98.2 (CH_2), 118.9 (CH_2), 131.7 (CH), 161.5 (C); *m*/*z* (CI) 332.0578 (MH^+. $C_{12}H_{21}O_3NCl_3$ requires 332.0587), 300 (42%), 262 (100), 238 (18), 202 (21) and 167 (49).

(3*R*,4*S*)-3-(Trichloromethylcarbonylamino)-4-(methoxymethoxy)-5-phenylpenta-1-ene (33a). 54% yield; ν_{max}/cm^{-1} (neat) 3273 (NH), 2943 (CH), 1711 (CO), 1513, 1143, 1027, 820, 699; $[\alpha]_D^{21}$ +59.1 (*c* 1.7, CH_2Cl_2); δ_H (400 MHz, $CDCl_3$) 2.82 (1H, dd, *J* 14.0, 5.2 Hz, 5-*H*H), 2.93 (1H, dd, *J* 14.0, 8.8 Hz, 5-H*H*), 3.39 (3H, s, OMe), 3.86 (1H, ddd, *J* 8.4, 4.8, 2.0 Hz, 4-H), 4.36 (1H, d, *J* 6.8 Hz, OC*H*HO), 4.45 (1H, br t, *J* 7.6 Hz, 3-H), 4.60 (1H, d, *J* 6.8 Hz, OCH*H*O), 5.42 (1H, d, *J* 7.6 Hz, 1-*H*H), 5.45 (1H, br s, 1-H*H*), 5.92–6.02 (1H, m, 2-H), 7.21–7.36 (5H, m, Ph), 8.19 (1H, d, *J* 7.6 Hz, NH); δ_C (100 MHz, $CDCl_3$) 39.4 (CH_2), 55.8 (CH), 56.7 (CH_3), 84.4 (CH), 92.9 (C), 98.1 (CH_2), 119.7 (CH_2), 126.8 (CH), 128.6 (CH), 129.3 (CH), 131.4 (CH), 137.4 (C), 161.4 (C); *m*/*z* (CI) 366.0431 (MH^+. $C_{15}H_{19}O_3NCl_3$ requires 366.0431), 334 (100%), 300 (25), 272 (26), 236 (19) and 173 (33).

(3*R*,4*S*)-3-(Trichloromethylcarbonylamino)-4-(methoxymethoxy)-6-phenylhexa-1-ene (34a) and (2*E*,4*S*)-1-(Trichloromethylcarbonylamino)-4-(methoxymethoxy)-6-phenylhexa-2-ene (34c). 65% combined yield; **34a**: (Found: C, 50.5; H, 5.3; N, 3.7. $C_{16}H_{20}Cl_3NO_3$ requires C, 50.5; H, 5.3; N, 3.7%); ν_{max}/cm^{-1} (neat) 3277 (NH), 2939 (CH), 1713 (CO), 1514, 1141, 1031, 821; $[\alpha]_D^{18}$ +58.8 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.81–1.91 (1H, m, 5-*H*H), 1.95–2.05 (1H, m, 5-H*H*), 2.63–2.71 (1H, m, 6-*H*H), 2.79–2.86 (1H, m, 6-H*H*), 3.48 (3H, s, OMe), 3.59 (1H, ddd, *J* 8.6, 4.4, 2.0 Hz, 4-H), 4.43 (1H, br t, *J* 8.6 Hz, 3-H), 4.65 (1H, d, *J* 6.8 Hz, OC*H*HO), 4.81 (1H, d, *J* 6.8 Hz, OCH*H*O), 5.34 (1H, d, *J* 1.2 Hz, 1-*H*H), 5.38 (1H, br d, *J* 8.6 Hz, 1-H*H*), 5.89 (1H, ddd, *J* 17.2, 10.4, 8.6 Hz, 2-H), 7.19–7.39 (5H, m, Ph), 8.37 (1H, br d, *J* 8.6 Hz, NH); δ_C (100 MHz, $CDCl_3$) 31.9 (CH_2), 34.8 (CH_2), 56.0 (CH), 56.9 (CH_3), 83.5 (CH), 93.0 (C), 98.4 (CH_2), 119.2 (CH_2), 126.2 (CH), 128.4 (CH), 128.6 (CH), 131.5 (CH), 141.0 (C), 161.5 (C); *m*/*z* (CI) 380 (MH^+, 100%), 310 (63), 286 (12), 244 (16), 187 (66) and 157 (58); **34c**: ν_{max}/cm^{-1} (neat) 3085 (NH), 2947 (CH), 1718 (CO), 1656 (C=C), 1496, 1148, 1098, 1030, 970; $[\alpha]_D^{20}$ −82.1 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.83–2.04 (2H, m, 5-H_2), 2.73–2.83 (2H, m, 6-H_2), 3.43 (3H, s, OMe), 4.10 (3H, m, 4-H and 1-H_2), 4.61 (1H, d, *J* 6.8 Hz, OC*H*HO), 4.74 (1H, d, *J* 6.8 Hz, OCH*H*O), 5.72 (1H, dd, *J* 15.2, 7.2 Hz, 3-H), 5.86 (1H, dt, *J* 15.2, 6.4 Hz, 2-H), 7.23–7.35 (5H, m, Ph); δ_C (100 MHz, $CDCl_3$) 31.6 (CH_2), 37.1 (CH_2), 44.3 (CH_2), 55.6 (CH_3), 75.4 (CH), 94.1 (CH_2), 94.1 (C), 126.0 (CH), 128.4 (CH), 128.5 (CH), 128.8 (CH), 134.7 (CH), 141.8 (C), 163.1 (C); *m*/*z* (CI) 321 ($MH^+ - CH_3OCH_2O$, 6%), 284 (11), 225 (12), 193 (62) and 157 (100).

Allylic trichloroacetimidate synthesis and subsequent rearrangement with bis(acetonitrile)palladium(II) chloride and *p*-benzoquinone

Preparation of the trichloroacetimidate was carried out as described above. The allylic trichloroacetimidate was dissolved in THF (10 mL). Bis(acetonitrile)palladium(II) chloride (10 mol%) and *p*-benzoquinone (2.0 equiv.) were 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 the target compounds as colourless oils.

(3*R*,4*S*)-3-(Trichloromethylcarbonylamino)-4-(methoxymethoxy)-6-methylhepta-1-ene (32a). 73% yield; spectroscopic data as described above.

(3*R*,4*S*)-3-(Trichloromethylcarbonylamino)-4-(methoxymethoxy)-5-phenylpenta-1-ene (33a). 70% yield; spectroscopic data as described above.

(3*R*,4*S*)-3-(Trichloromethylcarbonylamino)-4-(methoxymethoxy)-6-phenylhexa-1-ene (34a). 69% yield; spectroscopic data as described above.

Ruthenium trichloride oxidation to carboxylic acids 35–38 and deprotection to β-hydroxy-α-amino acids 39–42

Sodium metaperiodate (4.1 equiv.) was dissolved in water (21 mL) and added to a solution of the allylic trichloroamide (1 mmol) in carbon tetrachloride (14 mL) and acetonitrile (14 mL). Ruthenium trichloride hydrate (5 mol%) was added and the mixture was stirred vigorously for 6 h before a further portion of sodium metaperiodate (1 equiv.) was added. The reaction mixture was stirred vigorously overnight and then extracted with dichloromethane (3 × 40 mL). The organic layers were combined, dried ($MgSO_4$) and concentrated to give a viscous oil. The products were used without further purification. The carboxylic acid (1 mmol) was dissolved in 6 M hydrochloric acid (20 mL) and heated under reflux overnight. The reaction mixture was then cooled before being extracted with diethyl ether (2 × 10 mL). The aqueous layer was concentrated to give a brown liquid. Purification was carried out using ion exchange chromatography column on Dowex® 50WX8-100 (20 g per mmol of substrate), eluting with 25% ammonia solution. Concentration gave the β-hydroxy-α-amino acids as white solids.

(2*S*,3*S*)-2-Amino-3-hydroxybutanoic acid (39). 84% yield for first step and 80% yield for second step; $[\alpha]_D^{21}$ +8.0 (*c* 1.0, H_2O); lit.[19] $[\alpha]_D^{22}$ +8.6 (*c* 1.0, H_2O); δ_H (400 MHz, D_2O) 1.17 (3H, d, *J* 6.8 Hz, 4-H_3), 3.98 (1H, d, *J* 3.6 Hz, 2-H), 4.24 (1H, qd, *J* 6.8, 3.6 Hz, 3-H); δ_C (100 MHz, D_2O) 16.1 (CH_3), 59.6 (CH), 65.3 (CH), 171.9 (C); *m*/*z* (CI) 119.0589 (MH^+. $C_4H_9O_3N$ requires 119.0582), 117 (11%), 85 (4), 81 (74) and 79 (100).

(2*S*,3*S*)-2-Amino-3-hydroxy-5-methylhexanoic acid (40). 78% yield for first step and 62% yield for second step; ν_{max}/cm^{-1} (neat) 3033 (OH and NH), 2960 (CH), 1667 (CO), 1406, 1339, 1136, 1053; $[\alpha]_D^{20}$ +13.7 (*c* 1.0, 1 M HCl); lit.[20] $[\alpha]_D$ +14.6 (*c* 1.0, 1 M HCl); δ_H (400 MHz, D_2O) 0.82 (3H, d, *J* 6.8 Hz, 6-H_3), 0.86 (3H, d, *J* 6.8 Hz, 5-CH_3), 1.11 (1H, ddd, *J* 14.0, 10.0, 2.8 Hz, 4-*H*H), 1.43 (1H, ddd, *J* 14.0, 10.0, 4.4 Hz, 4-H*H*), 1.63–1.71 (1H, m, 5-H), 3.75 (3H, d, *J* 3.2 Hz, 2-H), 4.12 (1H, dt, *J* 10.0, 3.2 Hz, 3-H); δ_C (100 MHz, D_2O) 20.3 (CH_3), 22.7 (CH_3), 23.9 (CH), 39.6 (CH_2), 59.8 (CH), 67.5 (CH), 171.7 (C); *m*/*z* (CI) 145 ($MH^+ - NH_2$, 20%), 131 (50), 117 (49) and 113 (100).

(2*S*,3*S*)-2-Amino-3-hydroxy-4-phenylbutanoic acid (41). 69% yield for first step and 80% yield for second step; ν_{max}/cm^{-1} (neat) 3364 (OH and NH), 2940 (CH), 1717 (CO), 1494, 1224, 1034, 742; $[\alpha]_D^{21}$ +8.6 (*c* 1.0, 1 M HCl); lit.[20] $[\alpha]_D$ +9.1 (*c* 1.0, 1 M HCl); δ_H (400 MHz, D_2O) 2.83 (1H, dd, *J* 14.0, 9.2 Hz, 4-*H*H), 2.93 (1H, dd, *J* 14.0, 4.8 Hz, 4-H*H*), 4.03 (1H, d, *J* 2.8 Hz, 2-H), 4.22 (1H, ddd, *J* 9.2, 4.8, 2.8 Hz, 3-H), 7.12–7.31 (5H, m, Ph); δ_C (100 MHz, D_2O) 38.5 (CH_2), 57.0 (CH), 71.0 (CH), 126.9 (CH), 128.7 (CH), 129.3 (CH), 137.3 (C), 169.6 (C); *m*/*z* (CI) 196.0974 (MH^+. $C_{10}H_{14}O_3N$ requires 196.0974), 167 (16%), 139 (37) and 121 (21).

(2*S*,3*S*)-2-Amino-3-hydroxy-5-phenylpentanoic acid (42)[9b]. 81% yield for first step and 60% yield for second step; ν_{max}/cm^{-1} (neat) 3388 (OH and NH), 2913 (CH), 1729 (CO), 1495, 1218,

1036; $[a]_D^{19}$ +14.7 (*c* 0.4, 2 M HCl); δ_H (400 MHz, D_2O) 1.73–1.83 (2H, m, 4-CH_2), 2.53–2.63 (1H, m, 5-*H*H), 2.74 (1H, ddd, *J* 14.0, 8.8, 5.2 Hz, 5-H*H*), 3.89 (1H, d, *J* 3.6 Hz, 2-H), 3.93 (1H, dt, *J* 8.8, 3.6 Hz, 3-H), 7.09–7.26 (5H, m, Ph); δ_C (100 MHz, D_2O) 31.2 (CH_2), 33.2 (CH_2), 58.1 (CH), 68.6 (CH), 126.2 (CH), 128.5 (CH), 128.7 (CH), 141.3 (C), 169.9 (C); *m*/*z* (CI) 210 (MH^+, 12%), 175 (100), 144 (28) and 113 (34).

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