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# Asymmetric synthesis of allylic secondary alcohols: a new general approach for the preparation of α-amino acids

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ABSTRACT

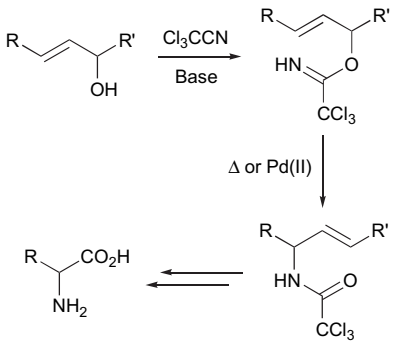
A new general approach for the synthesis of optically active α-amino acids has been developed. The key steps involve a ruthenium catalysed cross-coupling reaction to give a range of α,β-unsaturated ketones, which were then reduced to allylic secondary alcohols in the presence of a chiral CBS oxazaborolidine. A thermal Overman rearrangement was used to prepare a series of allylic trichloroacetimidates and these were converted under standard conditions to the target α-amino acids in good overall yields.



## 1. Introduction

The crucial role and vital importance of α-amino acids both as structural building blocks for peptides and proteins and for numerous biological functions are well established.[1] As well as the 20 proteinogenic α-amino acids, a significant number of structurally varied analogues have been found in nature from sources such as bacteria and fungi.[2] These have been used as key synthetic building blocks for the preparation of a wide range of biologically and pharmacologically active compounds, which are employed in the pharmaceutical, agrochemical and food industries.[3] Furthermore, modified α-amino acids are being increasingly used for the preparation of synthetic enzymes, hormones and immunostimulants as well as finding application as biological probes.[4] Structurally hindered α-amino acids are also utilised in the design of new peptides and peptidomimetics, which have enhanced metabolic stability.[5] This widespread application of α-amino acids in many disciplines has resulted in the continued development of new methods for their synthesis.[6]

A strategy commonly employed for the synthesis of a wide range of highly functionalised α-amino acids involves the thermal or palladium-catalysed Overman rearrangement of allylic trichloroacetimidates[7] followed by oxidation of the resulting alkene moiety to the corresponding carboxylic acid (Scheme 1).[8]




**Scheme 1.** Synthesis of α-amino acids using the Overman rearrangement.

This approach can be used for the synthesis of optically active α-amino acids using either allylic alcohols prepared from the chiral pool[8b–d,g,j–n] or chiral palladium(II)-catalysts during the Overman rearrangement.[8i] In addition to these methods, Walsh and coworkers generated a series of allylic secondary alcohols in excellent enantioselectivity by the addition of vinylzinc reagents to benzaldehyde in the presence of catalytic amounts of an isoborneol-derived amino alcohol.[8h] Overman rearrangement and oxidation then gave the α-amino acids in good yields. This remains the only reported example of the use of asymmetric synthesis for the general preparation of optically active allylic secondary alcohols for direct application via the Overman rearrangement for α-amino acid synthesis.

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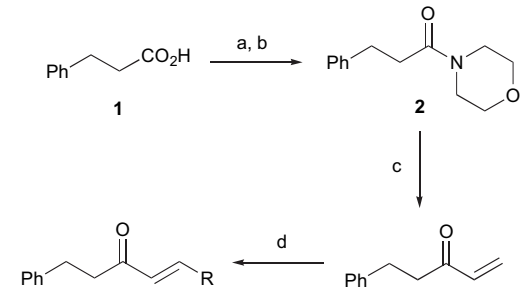
We were interested in developing an alternative approach for the general asymmetric synthesis of optically active allylic secondary alcohols for application in α-amino acid synthesis. We now report such an approach using cross-metathesis for the synthesis of a series of α,β-unsaturated ketones, which were then subjected to asymmetric reduction using a CBS oxazaborolidine.[9] The conversion of these optically active allylic secondary alcohols to α-amino acids via the Overman rearrangement is also described.

## 2. Results and discussion

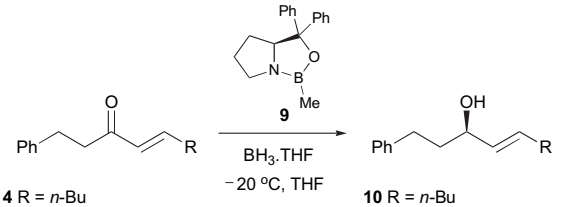
The initial stage of this work focused on a short and efficient route to the key α,β-unsaturated ketones from hydrocinnamic acid as shown in Scheme 2. Hydrocinnamic acid **1** was selected as the starting material as it is an inexpensive and readily available carboxylic acid with a side-chain unlikely to participate in any of the subsequent reactions. Hydrocinnamic acid **1** was converted to the morpholine amide **2** in 94% yield by conversion to the acid chloride followed by reaction with morpholine.[10] Treatment of **2** with vinylmagnesium bromide gave the key cross metathesis partner, vinyl ketone **3** in 74% yield. Cross metathesis of **3** with a series of terminal alkenes was then done using Grubbs second generation catalyst[11] (4–5 mol %), which gave the corresponding *E*-alkenes **4**–**8** in modest to high yields (47–89%). Analysis of the crude material from the cross metathesis reactions by $^1$H NMR spectroscopy showed the presence of only the *E*-alkenes highlighting the excellent stereoselectivity achieved using these types of cross metathesis partners.[12]




**Scheme 2.** Reagents and conditions: a. $SOCl_2$ (neat), rt; b. morpholine, $CH_2Cl_2$, 0 °C to Δ, 94% over two steps; c. vinylmagnesium bromide solution (1.0 M in THF), THF, 0 °C, 74%; d. Grubbs second generation catalyst, $CH_2Cl_2$, Δ, $H_2C$=CHR.

The next stage involved the asymmetric reduction of α,β-unsaturated ketones **4**–**8** using CBS oxazaborolidine **9** (Table 1). Optimised conditions were initially developed using (*E*)-1-phenylnon-4-en-3-one **4**. The use of catalytic amounts of CBS oxazaborolidines such as **9** for the asymmetric reduction of ketones is well known and thus, our first attempt under standard conditions employed 0.2 equiv of **9** (entry 1).[13] However, this gave allylic alcohol **10** in only 57% yield and in 31% enantiomeric excess.[14] The use of 0.5 equiv of **9** led to a substantial increase in both the yield and enantioselectivity (entry 2). The best results were obtained using a stoichiometric amount of **9**, which gave allylic alcohol **10** in 99% yield and 84% enantiomeric excess (entry 3). As a stoichiometric amount of **9** was required for generation of allylic alcohol **10** with high enantioselectivity, these conditions were used to reduce the remaining α,β-unsaturated ketones (entries 4–7). This gave allylic

**Table 1**
Asymmetric reduction of α,β-unsaturated ketones **4**–**8** using (*S*)-(−)-2-methyl-CBS-oxazaborolidine **9**




**4** R = *n*-Bu
**5** R = $CH_2CH_2Ph$
**6** R = $CH_2t$-Bu
**7** R = $CH_2CH_2CH_2CN$
**8** R = (*S*)-$CH_2CH(OTBDMS)CH_3$

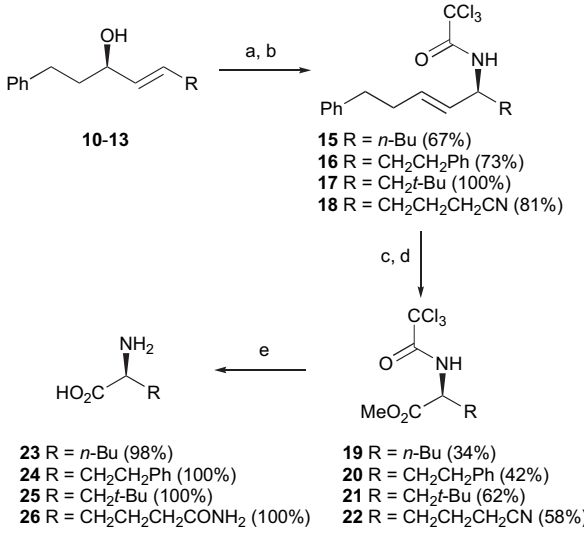
**10** R = *n*-Bu
**11** R = $CH_2CH_2Ph$
**12** R = $CH_2t$-Bu
**13** R = $CH_2CH_2CH_2CN$
**14** R = (*S*)-$CH_2CH(OTBDMS)CH_3$

| Entry | R | **9** (equiv) | Yield[a] (%) | ee[b] (%) |
|---|---|---|---|---|
| 1 | $CH_2CH_2CH_2CH_3$ | 0.2 | 57 | 31 |
| 2 | $CH_2CH_2CH_2CH_3$ | 0.5 | 100 | 71 |
| 3 | $CH_2CH_2CH_2CH_3$ | 1.0 | 99 | 84 |
| 4 | $CH_2CH_2Ph$ | 1.0 | 69 | 75 |
| 5 | $CH_2C(CH_3)_3$ | 1.0 | 77 | 69 |
| 6 | $CH_2CH_2CH_2CN$ | 1.0 | 63 | 87 |
| 7 | (*S*)-$CH_2CH(OTBDMS)CH_3$ | 1.0 | 87 | 100[c] |

[a] Isolated yields.
[b] Determined by chiral HPLC.
[c] Single diastereomer.

alcohols **11**–**13** in high yields (63–77%) and enantioselectivities (69–87%, entries 4–6). Reduction of chiral α,β-unsaturated ketone **8** gave allylic alcohol **14** in 87% yield and as a single diastereomer (entry 7).

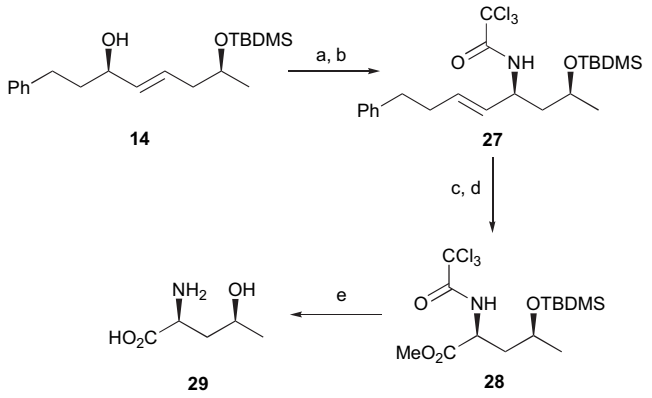
The optically active allylic alcohols **10**–**13** were then converted to the corresponding allyic trichloroacetamides **15**–**18** by preparation of the allylic trichloroacetimidates followed by an Overman rearrangement (Scheme 3). Initially, the Overman rearrangement was carried out using bis(acetonitrile)palladium(II) chloride.[15] This generated relatively complex mixtures, which yielded the allylic trichloroacetamides in only modest yields (e.g., 39% for **15**). Thermal rearrangement in the presence of potassium carbonate was more effective and gave allylic trichloroacetamides **15**–**18** more cleanly and in higher yields over the two steps (67–100%).[16] Oxidation of the allylic trichloroacetamides was carried out according




**Scheme 3.** Reagents and conditions: a. $Cl_3CCN$, DBU, $CH_2Cl_2$; b. Δ, $K_2CO_3$, *p*-xylene; c. $RuCl_3 \cdot xH_2O$, $NaIO_4$, $CCl_4$, MeCN, $H_2O$; d. $SOCl_2$, MeOH, Δ; e. 6 M HCl, Δ.

to the Sharpless protocol using catalytic ruthenium(III) trichloride hydrate and sodium metaperiodate.[17] The resulting carboxylic acids were then converted to methyl esters **19**–**22** before isolation and purification. Finally, deprotection under standard acidic conditions gave the desired α-amino acids **23**–**26** in good overall yield.[18] It should be noted that acid hydrolysis of **22** also led to conversion of the side-chain nitrile to the corresponding amide **26**.

In a similar fashion, allylic trichloroacetimidate **27** was formed in 87% yield (over two steps) from **14** using a thermal Overman rearrangement (Scheme 4). Attempted oxidation of **27** using the standard Sharpless ruthenium(III)/sodium metaperiodate protocol resulted in very low yields of the corresponding carboxylic acid and subsequent methyl ester. Therefore, a modified procedure using potassium permanganate[19] was employed and the resulting carboxylic acid was converted to methyl ester **28** using trimethylsilyldiazomethane. Acid mediated deprotection of **28** gave (2*S*,4*S*)-γ-hydroxynorvaline **29** (30% yield over the three steps), which showed optical activity and NMR spectra consistent with published values.[20]




**Scheme 4.** Reagents and conditions: a. $Cl_3CCN$, DBU, $CH_2Cl_2$; b. Δ, $K_2CO_3$, *p*-xylene, 87%; c. $KMnO_4$, $NaIO_4$, $K_2CO_3$, *t*-BuOH, $H_2O$; d. $TMSCHN_2$, MeOH, toluene; e. 6 M HCl, Δ, 30% over three steps.

## 3. Conclusion

In summary, a new general approach for the preparation of optically active allylic secondary alcohols has been developed using a ruthenium catalysed cross metathesis reaction and a CBS oxazaborolidine mediated reduction as the key steps. Conversion to the allylic trichloroacetimidates followed by a thermal Overman rearrangement gave the corresponding allylic trichloroacetamides, which were oxidised and deprotected to give a series of α-amino acids. While we have synthesised only L-amino acids in this project, both enantiomers of CBS oxazaborolidine **9** are commercially available and hence, access to both L- and D-α-amino acids should be possible using this approach. Further application of this work for the preparation of novel non-proteinogenic α-amino acids is currently underway.

## 4. Experimental section

### 4.1. General methods

All reagents and starting materials were obtained from commercial sources and used as received. All dry solvents were purified using a PureSolv 500 MD solvent purification system. All reactions were performed under an atmosphere of argon unless otherwise mentioned. Flash column chromatography was carried out using Fisher matrix 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 tetramethylsilane as the standard. Proton and carbon assignments are based on two-dimensional COSY and DEPT experiments, respectively. Infrared spectra were recorded using sodium chloride or potassium chloride plates 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 $cm^2$ $g^{-1}$. The chiral HPLC methods were calibrated with their corresponding racemic mixtures.

*4.1.1. 1-Morpholin-4-yl-3-phenylpropan-1-one (**2**)*[21]. A stirred solution of hydrocinnamic acid **1** (0.50 g, 3.33 mmol) in thionyl chloride (1.20 mL, 16.7 mmol) was allowed to stir at room temperature for 4.5 h before being concentrated in vacuo. Toluene (2×20 mL) was used to azeotrope the residue to give 3-phenylpropionyl chloride as a yellow oil (0.55 g, 97%), which was used without further purification. $\delta_H$ (400 MHz, $CDCl_3$) 3.02 (2H, t, *J* 7.4 Hz, 3-$H_2$), 3.21 (2H, t, *J* 7.4 Hz, 2-$H_2$), 7.17–7.34 (5H, m, 5×ArH). A stirred solution of 3-phenylpropionyl chloride (0.55 g, 3.24 mmol) in dichloromethane (10 mL) was cooled to 0 °C, and morpholine (1.42 mL, 16.2 mmol) was added dropwise. The resulting suspension was heated under reflux for 20 h. The reaction mixture was allowed to cool to room temperature and dichloromethane (50 mL) was added. The organic layer was washed with water (2×30 mL) and then dried ($MgSO_4$), filtered and concentrated in vacuo. Purification was carried out by flash column chromatography and elution with 1:1 ethyl acetate/petroleum ether gave 1-morpholin-4-yl-3-phenylpropan-1-one **2** as a pale yellow oil (0.68 g, 94%). $R_f$ (50% EtOAc/petroleum ether) 0.17; $\delta_H$ (400 MHz, $CDCl_3$) 2.62 (2H, t, *J* 7.6 Hz, $CH_2$), 2.98 (2H, t, *J*, 7.6 Hz, $CH_2$), 3.36 (2H, t, *J* 4.4 Hz, $CH_2$), 3.51 (2H, t, *J* 4.4 Hz, $CH_2$), 3.60–3.65 (4H, m, 2×$CH_2$), 7.21–7.31 (5H, m, 5×ArH); $\delta_C$ (100 MHz, $CDCl_3$) 31.5 ($CH_2$), 34.9 ($CH_2$), 42.0 ($CH_2$), 46.0 ($CH_2$), 66.5 ($CH_2$), 66.9 ($CH_2$), 126.3 (CH), 128.5 (2×CH), 128.6 (2×CH), 141.1 (C), 171.0 (C); *m*/*z* (CI) 220 ($MH^+$, 100%), 219 (7), 172 (2), 130 (1), 81 (3).

*4.1.2. 5-Phenylpent-1-en-3-one (**3**)*[22]. A stirred solution of 1-morpholin-4-yl-3-phenylpropan-1-one **2** (0.55 g, 2.50 mmol) in THF (20 mL) was cooled to 0 °C before vinylmagnesium bromide solution (1.0 M in THF, 10 mL, 10 mmol) was added dropwise. The reaction mixture was stirred at 0 °C for 2 h before being quenched by pouring into glacial acetic acid (10 mL) and then concentrated in vacuo. The residue was then partitioned between dichloromethane (50 mL) and a saturated solution of ammonium chloride (50 mL) and the organic phase was dried ($MgSO_4$), filtered and concentrated in vacuo. Purification was carried out by flash column chromatography, and elution with 1:9 ethyl acetate/petroleum ether gave 5-phenylpent-1-en-3-one **3** as a colourless oil (0.30 g, 74%). $R_f$ (50% EtOAc/petroleum ether) 0.69; $\delta_H$ (400 MHz, $CDCl_3$) 2.89–2.98 (4H, m, 4-$H_2$ and 5-$H_2$), 5.83 (1H, d, *J* 10.8 Hz, 1-*H*H), 6.22 (1H, d, *J* 17.6 Hz, 1-H*H*), 6.36 (1H, dd, *J* 17.6, 10.8 Hz, 2-H), 7.20–7.31 (5H, m, 5×ArH); $\delta_C$ (100 MHz, $CDCl_3$) 29.8 ($CH_2$), 41.2 ($CH_2$), 126.1 (CH), 128.3 ($CH_2$), 128.4 (2×CH), 128.5 (2×CH), 136.5 (CH), 141.1 (C), 199.8 (C); *m*/*z* (CI) 161 ($MH^+$, 100%), 160 (5), 91 (3).

*4.1.3. (5E)-9-Phenylnon-5-en-7-one (**4**)*[23]. To a stirred solution of Grubbs second generation catalyst (0.26 g, 0.31 mmol) in dichloromethane (20 mL), 5-phenylpent-1-en-3-one **3** (1.00 g, 6.24 mmol) dissolved in dichloromethane (10 mL) was added, followed by 1-hexene (1.55 mL, 12.5 mmol). The reaction mixture was then heated under reflux for 22 h before being concentrated in

vacuo and purified by flash column chromatography. Elution with 1:19 ethyl acetate/petroleum ether gave (5*E*)-9-phenylnon-5-en-7-one **4** as a brown oil (0.99 g, 75%). $R_f$ (20% EtOAc/petroleum ether) 0.68; $\delta_H$ (400 MHz, $CDCl_3$) 0.91 (3H, t, *J* 7.2 Hz, 1-$H_3$), 1.30–1.49 (4H, m, 2-$H_2$ and 3-$H_2$), 2.17–2.23 (2H, m, 4-$H_2$), 2.84–2.96 (4H, m, 8-$H_2$ and 9-$H_2$), 6.09 (1H, dt, *J* 15.6, 1.6 Hz, 6-H), 6.82 (1H, dt, *J* 15.6, 7.2 Hz, 5-H), 7.17–7.30 (5H, m, 5×ArH); $\delta_C$ (100 MHz, $CDCl_3$) 13.9 ($CH_3$), 22.3 ($CH_2$), 30.1 ($CH_2$), 30.2 ($CH_2$), 32.2 ($CH_2$), 41.6 ($CH_2$), 126.1 (CH), 128.4 (2×CH), 128.5 (2×CH), 130.3 (CH), 141.3 (C), 147.9 (CH), 199.7 (C); *m*/*z* (CI) 217 ($MH^+$, 100%), 203 (15), 189 (4), 159 (9), 97 (5), 85 (32), 69 (29).

*4.1.4. 1,7-Diphenylhept-3-en-5-one (**5**)*[24]. The reaction was carried out as described for **4** using 5-phenylpent-1-en-3-one **3** (0.50 g, 3.13 mmol), 4-phenyl-1-butene (0.94 mL, 6.27 mmol) and Grubbs second generation catalyst (0.11 g, 0.13 mmol). Purification by flash column chromatography, eluting with 3:17 diethyl ether/petroleum ether gave 1,7-diphenylhept-3-en-5-one **5** as a colourless oil (0.39 g, 47%). $R_f$ (20% EtOAc/petroleum ether) 0.53; $\delta_H$ (400 MHz, $CDCl_3$) 2.47–2.53 (2H, m, 2-$H_2$), 2.77 (2H, t, *J* 7.2 Hz, 1-$H_2$), 2.81–2.95 (4H, m, 6-$H_2$ and 7-$H_2$), 6.11 (1H, d, *J* 15.8 Hz, 4-H), 6.84 (1H, dt, *J* 15.8, 7.2 Hz, 3-H), 7.14–7.32 (10H, m, 10×ArH); $\delta_C$ (100 MHz, $CDCl_3$) 30.1 ($CH_2$), 34.1 ($CH_2$), 34.4 ($CH_2$), 41.7 ($CH_2$), 126.1 (CH), 126.2 (CH), 128.3 (2×CH), 128.4 (2×CH), 128.5 (4×CH), 130.7 (CH), 140.7 (C), 141.2 (C), 146.3 (CH), 199.5 (C); *m*/*z* (EI) 264 ($M^+$, 13%), 159 (54), 131 (8), 105 (15), 91 (100), 65 (12), 44 (49).

*4.1.5. (4E)-2,2-Dimethyl-8-phenyloct-4-en-6-one (**6**).* The reaction was carried out as described for **4** using 5-phenylpent-1-en-3-one **3** (0.77 g, 4.80 mmol), 4,4-dimethyl-1-pentene (1.40 mL, 9.60 mmol) and Grubbs second generation catalyst (0.16 g, 0.19 mmol). Purification was carried out by flash column chromatography, and elution with 1:9 ethyl acetate/petroleum ether gave (4*E*)-2,2-dimethyl-8-phenyloct-4-en-6-one **6** as a yellow oil (0.65 g, 58%). $R_f$ (20% EtOAc/petroleum ether) 0.65; $\nu_{max}$ (NaCl) 2960 (CH), 1670 (CO), 1474, 1367, 1095, 908, 734 $cm^{-1}$; $\delta_H$ (400 MHz, $CDCl_3$) 0.92 (9H, s, $C(CH_3)_3$), 2.08 (2H, d, *J* 8.0 Hz, 3-$H_2$), 2.85–2.96 (4H, m, 7-$H_2$ and 8-$H_2$), 6.08 (1H, d, *J* 15.6 Hz, 5-H), 6.84 (1H, dt, *J* 15.6, 8.0 Hz, 4-H), 7.17–7.31 (5H, m, 5×ArH); $\delta_C$ (100 MHz, $CDCl_3$) 29.4 (3×$CH_3$), 30.2 ($CH_2$), 31.5 (C), 41.7 ($CH_2$), 47.0 ($CH_2$), 126.1 (CH), 128.4 (2×CH), 128.5 (2×CH), 132.3 (CH), 141.3 (C), 145.2 (CH), 199.4 (C); *m*/*z* (EI) 230 ($M^+$, 12%), 215 (11), 174 (6), 159 (100), 105 (18), 91 (46), 84 (42), 57 (56); HRMS (EI): $M^+$, found 230.1674. $C_{16}H_{22}O$ requires 230.1671.

*4.1.6. (4E)-1-Nitrile-8-phenyloct-4-en-6-one (**7**).* To a stirred solution of 5-phenylpent-1-en-3-one **3** (0.97 g, 6.07 mmol) in dichloromethane (25 mL), 5-hexenenitrile (1.2 mL, 10.6 mmol), Grubbs second generation catalyst (0.21 g, 0.24 mmol) was added. The reaction mixture was then heated under reflux for 22 h before further Grubbs second generation catalyst (0.10 g, 0.12 mmol) was added and the reaction was stirred at 45 °C for 50 h. Then, further Grubbs second generation catalyst (0.10 g, 0.12 mmol) was added and the reaction was stirred at 45 °C for 72 h before further Grubbs second generation catalyst (0.05 g, 0.06 mmol) was added. The reaction was then stirred at 45 °C for a further 24 h before being concentrated in vacuo. Purification was carried out by flash column chromatography, and elution with 1:3 ethyl acetate/petroleum ether gave (4*E*)-1-nitrile-8-phenyloct-4-en-6-one **7** as a pale brown oil (0.53 g, 53%). $R_f$ (20% EtOAc/petroleum ether) 0.15; $\nu_{max}$ (NaCl) 3028 (CH), 2934 (CH), 2246 (CN), 1669 (CO), 1453, 978, 701 $cm^{-1}$; $\delta_H$ (400 MHz, $CDCl_3$) 1.78–1.87 (2H, m, 1-$H_2$), 2.32–2.42 (4H, m, 2-$H_2$ and 3-$H_2$), 2.84–2.98 (4H, m, 7-$H_2$ and 8-$H_2$), 6.13 (1H, d, *J* 15.8 Hz, 5-H), 6.73 (1H, dt, *J* 15.8, 6.8 Hz, 4-H), 7.16–7.33 (5H, m, 5×Ar); $\delta_C$ (100 MHz, $CDCl_3$) 16.7 ($CH_2$), 23.8 ($CH_2$), 30.0 ($CH_2$), 31.0 ($CH_2$), 42.2 ($CH_2$), 119.0 (C), 126.2 (CH), 128.4 (2×CH), 128.5 (2×CH), 131.6 (CH), 141.1 (C), 143.9 (CH), 199.1 (C); *m*/*z* (EI) 227 ($M^+$, 3%), 207 (3), 159 (20), 122 (9), 105 (16), 91 (16), 77 (18); HRMS (EI): $M^+$, found 227.1308. $C_{15}H_{17}NO$ requires 227.1310.

*4.1.7. (4S)-4-[(tert-Butyldimethylsilyl)oxy]-1-pentene*[25]. To a stirred solution of (4*S*)-(+)-4-penten-2-ol (0.62 g, 7.23 mmol) in dichloromethane (30 mL), triethylamine (2.00 mL, 14.5 mmol) and 4-dimethylaminopyridine (0.09 g, 0.72 mmol) were added. This solution was then cooled to 0 °C before *tert*-butyldimethylsilyl chloride (1.42 g, 9.40 mmol) was added slowly. The resulting reaction mixture was allowed to stir at 0 °C for 0.2 h, and then at room temperature for 21 h before water (50 mL) and dichloromethane (20 mL) were added. The layers were separated and the aqueous layer was further extracted using dichloromethane (30 mL). The combined organic layers were then washed with a saturated solution of aqueous copper sulfate (2×40 mL) and water (40 mL) before being dried ($MgSO_4$), filtered and concentrated in vacuo. Purification was carried out by flash column chromatography, and elution with 1:30 diethyl ether/petroleum ether gave (4*S*)-4-[(*tert*-butyldimethylsilyl)oxy]-1-pentene as a colourless oil (0.75 g, 52%). $R_f$ (20% EtOAc/petroleum ether) 0.62; $[\alpha]_D^{24}$ +18.1 (*c* 1.0, $CHCl_3$); $\delta_H$ (400 MHz, $CDCl_3$) 0.05 (6H, s, 2×$SiCH_3$), 0.89 (9H, s, $SiC(CH_3)_3$), 1.13 (3H, d, *J* 6.0 Hz, 5-$H_3$), 2.11–2.25 (2H, m, 3-$H_2$), 3.84 (1H, q, *J* 6.0 Hz, 4-H), 4.99–5.06 (2H, m, 1-$H_2$), 5.75–5.86 (1H, m, 2-H); $\delta_C$ (100 MHz, $CDCl_3$) −5.7 ($CH_3$), −5.6 ($CH_3$), 17.2 (C), 22.4 ($CH_3$), 24.9 (3×$CH_3$), 43.3 ($CH_2$), 67.4 (CH), 115.5 ($CH_2$), 134.6 (CH); *m*/*z* (CI) 201 ($MH^+$, 4%), 193 (9), 167 (8), 151 (7), 113 (29), 95 (22), 69 (100).

*4.1.8. (2S,4E)-2-[(tert-Butyldimethylsilyl)oxy]-8-phenyloct-4-en-6-one (**8**).* The reaction was carried out as described for **4** using 5-phenylpent-1-en-3-one **3** (0.10 g, 0.62 mmol), (4*S*)-4-[(*tert*-butyldimethylsilyl)oxy]-1-pentene (0.15 g, 0.75 mmol) and Grubbs second generation catalyst (0.03 g, 0.03 mmol). Purification was carried out by flash column chromatography, and elution with 1:19 diethyl ether/petroleum ether gave (2*S*,4*E*)-2-[(*tert*-butyldimethylsilyl)oxy]-8-phenyloct-4-en-6-one **8** as a colourless oil (0.18 g, 89%). $R_f$ (20% EtOAc/petroleum ether) 0.59; $\nu_{max}$ (NaCl) 2929 (CH), 1674 (CO), 1632, 1454, 1375, 1256, 1128, 1003, 836 $cm^{-1}$; $[\alpha]_D^{22}$ +14.2 (*c* 1.0, $CHCl_3$); $\delta_H$ (400 MHz, $CDCl_3$) 0.03 (3H, s, $SiCH_3$), 0.04 (3H, s, $SiCH_3$), 0.87 (9H, s, $SiC(CH_3)_3$), 1.14 (3H, d, *J* 6.5 Hz, 1-$H_3$), 2.32 (2H, t, *J* 6.5 Hz, 3-$H_2$), 2.84–2.96 (4H, m, 7-$H_2$ and 8-$H_2$), 3.92 (1H, sex, *J* 6.5 Hz, 2-H), 6.10 (1H, d, *J* 16.0 Hz, 5-H), 6.83 (1H, dt, *J* 16.0, 6.5 Hz, 4-H), 7.18–7.30 (5H, m, 5×ArH); $\delta_C$ (100 MHz, $CDCl_3$) −4.7 ($CH_3$), −4.4 ($CH_3$), 18.1 (C), 23.9 ($CH_3$), 25.9 (3×$CH_3$), 30.1 ($CH_2$), 41.5 ($CH_2$), 42.8 ($CH_2$), 67.7 (CH), 126.1 (CH), 128.4 (2×CH), 128.6 (2×CH), 132.3 (CH), 141.3 (C), 144.5 (CH), 199.4 (C); *m*/*z* (CI) 333 ($MH^+$, 81%), 275 (11), 237 (9), 201 (9), 181 (9), 159 (43), 137 (12), 97 (53), 71 (100); HRMS (CI): $MH^+$, found 333.2253. $C_{20}H_{33}O_2Si$ requires 333.2250.

*4.1.9. (5E,7R)-9-Phenylnon-5-en-7-ol (**10**)*[26]. A stirred solution of (5*E*)-9-phenylnon-5-en-7-one **4** (0.29 g, 1.30 mmol) in THF (10 mL) was cooled to −20 °C before (*S*)-(−)-2-methyl-CBS-oxazaborolidine solution (1.0 M in toluene) (1.30 mL, 1.30 mmol) was added, followed by borane–THF complex solution (1.0 M in THF) (4.00 mL, 4.00 mmol). The reaction mixture was then stirred at −20 °C for 2.5 h before being quenched by the slow addition of methanol (15 mL). Once gas evolution ceased, the reaction mixture was concentrated in vacuo and purification was carried out by flash column chromatography. Elution with 1:19 ethyl acetate/petroleum ether gave (5*E*,7*R*)-9-phenylnon-5-en-7-ol **10** as a colourless oil (0.29 g, 99%). Chiral HPLC (Chiralcel IB column) analysis using 2% isopropanol in hexane as the elution solvent indicated 84% ee. $R_f$ (20% EtOAc/petroleum ether) 0.39; $\delta_H$ (400 MHz, $CDCl_3$) 0.90 (3H, t, *J* 7.2 Hz, 1-$H_3$), 1.26–1.40 (4H, m, 2-$H_2$ and 3-$H_2$), 1.45 (1H, br s, OH), 1.75–1.93 (2H, m, 4-$H_2$), 1.99–2.07 (2H, m, 8-$H_2$), 2.62–2.79 (2H, m,

9-$H_2$), 4.09 (1H, m, 7-H), 5.49 (1H, ddt, *J* 15.2, 6.8, 1.2 Hz, 6-H), 5.66 (1H, dt, *J* 15.2, 6.8 Hz, 5-H), 7.16–7.30 (5H, m, 5×ArH); $\delta_C$ (100 MHz, $CDCl_3$) 14.0 ($CH_3$), 22.2 ($CH_2$), 31.4 ($CH_2$), 31.8 ($CH_2$), 31.9 ($CH_2$), 38.9 ($CH_2$), 72.5 (CH), 125.8 (CH), 128.4 (3×CH), 128.5 (2×CH), 132.7 (CH), 142.0 (C); *m*/*z* (CI) 201 ($MH^+-H_2O$, 100%), 187 (11), 167 (4), 133 (6), 117 (7), 91 (13).

*4.1.10. (3E,5R)-1,7-Diphenylhept-3-en-5-ol (**11**).* The reaction was carried out as described for **10** using 1,7-diphenylhept-3-en-5-one **5** (0.19 g, 0.72 mmol), (*S*)-(−)-2-methyl-CBS-oxazaborolidine solution (1.0 M in toluene) (0.72 mL, 0.72 mmol) and borane–THF complex solution (1.0 M in THF) (2.20 mL, 2.20 mmol). Purification by flash column chromatography with 3:17 ethyl acetate/petroleum ether gave (3*E*,5*R*)-1,7-diphenylhept-3-en-5-ol **11** as a colourless oil (0.13 g, 69%). Chiral HPLC (Chiralcel IB column) analysis using 4% isopropanol in hexane as the elution solvent indicated 75% ee. $R_f$ (20% EtOAc/petroleum ether) 0.32; $\nu_{max}$ (NaCl) 3356 (OH), 2925 (CH), 1602, 1454, 970, 698 $cm^{-1}$; $\delta_H$ (400 MHz, $CDCl_3$) 1.40 (1H, d, *J* 3.2 Hz, OH), 1.70–1.90 (2H, m, 6-$H_2$), 2.37 (2H, dt, *J* 7.6, 6.8 Hz, 2-$H_2$), 2.57–2.73 (4H, m, 1-$H_2$ and 7-$H_2$), 4.02–4.10 (1H, m, 5-H), 5.50 (1H, dd, *J* 15.6, 7.0 Hz, 4-H), 5.69 (1H, dt, *J* 15.6, 6.8 Hz, 3-H), 7.15–7.30 (10H, m, 10×ArH); $\delta_C$ (100 MHz, $CDCl_3$) 31.7 ($CH_2$), 33.9 ($CH_2$), 35.6 ($CH_2$), 38.7 ($CH_2$), 72.3 (CH), 125.8 (CH), 125.9 (CH), 128.3 (2×CH), 128.4 (2×CH), 128.5 (4×CH), 131.4 (CH), 133.5 (CH), 141.6 (C), 142.0 (C); *m*/*z* (EI) 266 ($M^+$, 3%), 248 (10), 161 (21), 144 (28), 105 (42), 91 (100), 83 (18); HRMS (EI): $M^+$, found 266.1674. $C_{19}H_{22}O$ requires 266.1671.

*4.1.11. (4E,6R)-2,2-Dimethyl-8-phenyloct-4-en-6-ol (**12**).* The reaction was carried out as described for **10** using (2*E*)-2,2-dimethyl-8-phenyloct-4-en-6-one **6** (0.20 g, 0.87 mmol), (*S*)-(−)-2-methyl-CBS-oxazaborolidine solution (1.0 M in toluene) (0.90 mL, 0.90 mmol) and borane–THF complex solution (1.0 M in THF) (2.60 mL, 2.60 mmol). Purification by flash column chromatography with 1:9 ethyl acetate/petroleum ether gave (4*E*,6*R*)-2,2-dimethyl-8-phenyloct-4-en-6-ol **12** as a colourless oil (0.16 g, 77%). Chiral HPLC (Chiralcel IB column) analysis using 3% isopropanol in hexane as the elution solvent indicated 69% ee. $R_f$ (20% EtOAc/petroleum ether) 0.44; $\nu_{max}$ (NaCl) 3609 (OH), 3019 (CH), 1475, 1216, 772 $cm^{-1}$; $\delta_H$ (400 MHz, $CDCl_3$) 0.89 (9H, s, $C(CH_3)_3$), 1.45 (1H, d, *J* 3.6 Hz, OH), 1.76–1.98 (4H, m, 3-$H_2$ and 7-$H_2$), 2.63–2.76 (2H, m, 8-$H_2$), 4.07–4.14 (1H, m, 4-H), 5.49 (1H, dd, *J* 15.2, 7.2 Hz, 5-H), 5.69 (1H, dt, *J* 15.2, 7.6 Hz, 4-H), 7.16–7.31 (5H, m, 5×ArH); $\delta_C$ (100 MHz, $CDCl_3$) 29.3 (3×$CH_3$), 30.9 (C), 31.8 ($CH_2$), 38.9 ($CH_2$), 46.7 ($CH_2$), 72.5 (CH), 125.8 (CH), 128.3 (2×CH), 128.4 (2×CH), 129.5 (CH), 135.1 (CH), 142.0 (C); *m*/*z* (EI) 232 ($M^+$, 7%), 214 (9), 161 (26), 143 (24), 127 (46), 91 (100), 83 (51), 57 (98); HRMS (EI): $M^+$, found 232.1830. $C_{16}H_{24}O$ requires 232.1827.

*4.1.12. (4E,6R)-1-Nitrile-8-phenyloct-4-en-6-ol (**13**).* The reaction was carried out as described for **10** using (4*E*)-1-nitrile-8-phenyloct-4-en-6-one **7** (0.15 g, 0.65 mmol), (*S*)-(−)-2-methyl-CBS-oxazaborolidine solution (1.0 M in toluene) (0.65 mL, 0.65 mmol) and borane–THF complex solution (1.0 M in THF) (1.95 mL, 1.95 mmol). Purification was carried out by flash column chromatography, and elution with 3:7 ethyl acetate/petroleum ether gave (4*E*,6*R*)-1-nitrile-8-phenyloct-4-en-6-ol as a colourless oil (0.10 g, 63%). Chiral HPLC (Chiralcel IB column) analysis using 6% isopropanol in hexane as the elution solvent indicated 87% ee. $R_f$ (20% EtOAc/petroleum ether) 0.09; $\nu_{max}$ (NaCl) 3448 (OH), 2932 (CH), 2251 (CN), 1454, 910, 731 $cm^{-1}$; $\delta_H$ (400 MHz, $CDCl_3$) 1.47–1.51 (1H, m, OH), 1.71–1.77 (2H, m, 2-$H_2$), 1.78–1.93 (2H, m, 7-$H_2$), 2.19–2.25 (2H, m, 3-$H_2$), 2.35 (2H, t, *J* 7.2 Hz, 1-$H_2$), 2.62–2.77 (2H, m, 8-$H_2$), 4.07–4.14 (1H, m, 6-H), 5.59–5.62 (2H, m, 4-H and 5-H), 7.17–7.32 (5H, m, 5×ArH); $\delta_C$ (100 MHz, $CDCl_3$) 16.5 ($CH_2$), 24.7 ($CH_2$), 31.0 ($CH_2$), 31.8 ($CH_2$), 38.8 ($CH_2$), 72.1 (CH), 119.6 (C), 125.9 (2×CH), 128.5 (2×CH), 129.0 (2×CH), 135.1 (CH), 141.8 (C); *m*/*z* (CI) 230 ($MH^+$, 10%), 212 (100), 184 (8), 149 (4), 107 (27), 79 (30); HRMS (CI): $MH^+$, found 230.1555. $C_{15}H_{20}NO$ requires 230.1545.

*4.1.13. (2S,4E,6R)-2-[(tert-Butyldimethylsilyl)oxy]-8-phenyloct-4-en-6-ol (**14**).* The reaction was carried out as described for **10** using (2*S*,4*E*)-2-[(*tert*-butyldimethylsilyl)oxy]-8-phenyloct-4-en-6-one **8** (0.50 g, 1.50 mmol), (*S*)-(−)-2-methyl-CBS-oxazaborolidine solution (1.0 M in toluene) (1.50 mL, 1.50 mmol) and borane–THF complex solution (1.0 M in THF) (7.52 mL, 7.52 mmol). Purification by flash column chromatography with 3:17 diethyl ether/petroleum ether gave (2*S*,4*E*,6*R*)-2-[(*tert*-butyldimethylsilyl)oxy]-8-phenyloct-4-en-6-ol **14** as a colourless oil (0.44 g, 87%). $R_f$ (20% EtOAc/petroleum ether) 0.43; $\nu_{max}$ (NaCl) 3395 (OH), 2961 (CH), 1639, 1455, 1254, 1084, 835, 774 $cm^{-1}$; $[\alpha]_D^{22}$ +17.1 (*c* 1.0, $CHCl_3$); $\delta_H$ (400 MHz, $CDCl_3$) 0.05 (6H, s, 2×$SiCH_3$), 0.88 (9H, s, $SiC(CH_3)_3$), 1.12 (3H, d, *J* 6.0 Hz, 1-$H_3$), 1.43 (1H, br s, OH), 1.76–1.93 (2H, m, 7-$H_2$), 2.10–2.25 (2H, m, 3-$H_2$), 2.63–2.76 (2H, m, 8-$H_2$), 3.83 (1H, sex, *J* 6.0 Hz, 2-H), 4.05–4.13 (1H, m, 6-H), 5.53 (1H, dd, *J* 15.4, 6.9 Hz, 5-H), 5.67 (1H, dt, *J* 15.4, 6.9 Hz, 4-H), 7.15–7.31 (5H, m, 5×ArH); $\delta_C$ (100 MHz, $CDCl_3$) −4.7 ($CH_3$), −4.5 ($CH_3$), 18.2 (C), 23.5 ($CH_3$), 25.9 (3×$CH_3$), 31.8 ($CH_2$), 38.8 ($CH_2$), 42.6 ($CH_2$), 68.5 (CH), 75.5 (CH), 125.8 (CH), 128.4 (2×CH), 128.5 (2×CH), 129.0 (CH), 135.0 (CH), 142.0 (C); *m*/*z* (FAB) 357 ($MNa^+$, 100%), 333 (21), 268 (18), 228 (17), 186 (18), 160 (86), 148 (38), 117 (78), 105 (24), 75 (77); HRMS (FAB): $MNa^+$, found 357.2221. $C_{20}H_{34}NaO_2Si$ requires 357.2226.

*4.1.14. (5S,6E)-9-Phenyl-5-(trichloromethylcarbonylamino)non-6-ene (**15**).* A stirred solution of (5*E*,7*R*)-9-phenylnon-5-en-7-ol **10** (0.25 g, 1.20 mmol) in dichloromethane (10 mL) was cooled to 0 °C before 1,8-diazabicyclo[5.4.0]undec-7-ene (0.09 mL, 0.60 mmol) was added, followed by trichloroacetonitrile (0.18 mL, 1.80 mmol). The reaction mixture was stirred at 0 °C for 0.2 h, and then at room temperature for 26 h. The mixture was then filtered through a plug of silica and washed with diethyl ether (50 mL) and the filtrates were concentrated in vacuo to give a yellow oil (0.48 g). The crude residue was then dissolved in *p*-xylene (20 mL) and potassium carbonate (0.06 g) was added. The reaction mixture was then heated under reflux for 24 h before being concentrated in vacuo. Purification was carried out by flash column chromatography, and elution with 1:19 ethyl acetate/petroleum ether gave (5*S*,6*E*)-9-phenyl-5-(trichloromethylcarbonylamino)non-6-ene **15** as a colourless oil (0.28 g, 67%). $R_f$ (20% EtOAc/petroleum ether) 0.61; $\nu_{max}$ (NaCl) 3423 (NH), 2933 (CH), 1712 (CO), 1509, 908, 741 $cm^{-1}$; $\delta_H$ (400 MHz, $CDCl_3$) 0.89 (3H, t, *J* 7.0 Hz, 1-$H_3$), 1.21–1.36 (4H, m, 2-$H_2$ and 3-$H_2$), 1.54–1.59 (2H, m, 4-$H_2$), 2.37 (2H, dt, *J* 7.4, 7.4 Hz, 8-$H_2$), 2.70 (2H, t, *J* 7.4 Hz, 9-$H_2$), 4.29–4.36 (1H, m, 5-H), 5.35 (1H, dd, *J* 15.6, 6.4 Hz, 6-H), 5.69 (1H, dt, *J* 15.6, 7.4 Hz, 7-H), 6.43 (1H, br d, *J* 7.6 Hz, NH), 7.13–7.30 (5H, m, 5×ArH); $\delta_C$ (100 MHz, $CDCl_3$) 13.9 ($CH_3$), 22.4 ($CH_2$), 27.7 ($CH_2$), 34.0 ($CH_2$), 34.5 ($CH_2$), 35.4 ($CH_2$), 53.2 (CH), 92.9 (C), 125.9 (CH), 128.3 (2×CH), 128.5 (2×CH), 129.2 (CH), 132.2 (CH), 141.1 (C), 160.9 (C); *m*/*z* (CI) 362 ($MH^+$, 27%), 329 (46), 293 (80), 259 (35), 233 (76), 219 (100), 201 (36), 145 (51), 101 (25), 81 (48), 71 (46); HRMS (CI): $MH^+$, found 362.0842. $C_{17}H_{23}{}^{35}Cl_3NO$ requires 362.0845.

*4.1.15. (3S,4E)-1,7-Diphenyl-3-(trichloromethylcarbonylamino)hept-4-ene (**16**).* The reaction was carried out as described for **15** using (3*E*,5*R*)-1,7-diphenylhept-3-en-5-ol **11** (0.10 g, 0.37 mmol), 1,8-diazabicyclo[5.4.0]undec-7-ene (0.03 mL, 0.18 mmol) and trichloroacetonitrile (0.06 mL, 0.55 mmol). Purification was carried out by flash column chromatography, and elution with 1:9 ethyl acetate/petroleum ether gave (3*S*,4*E*)-1,7-diphenyl-3-(trichloromethylcarbonylamino)hept-4-ene **16** as a colourless oil (0.13 g, 73%). $R_f$ (20% EtOAc/petroleum ether) 0.53; $\nu_{max}$ (NaCl) 3422 (NH), 3019 (CH), 1713 (CO), 1509, 1216, 756 $cm^{-1}$; $\delta_H$ (400 MHz,

$CDCl_3$) 1.84–1.98 (2H, m, 2-$H_2$), 2.39–2.47 (2H, m, 6-$H_2$), 2.61 (2H, t, *J* 7.6 Hz, 1-$H_2$), 2.70 (2H, t, *J* 7.6 Hz, 7-$H_2$), 4.33–4.41 (1H, m, 3-H), 5.39 (1H, dd, *J* 15.6, 6.4 Hz, 4-H), 5.71 (1H, dt, *J* 15.6, 6.4 Hz, 5-H), 6.48 (1H, d, *J* 8.0 Hz, NH), 7.12–7.31 (10H, m, 10×ArH); $\delta_C$ (100 MHz, $CDCl_3$) 29.7 ($CH_2$), 32.0 ($CH_2$), 35.5 ($CH_2$), 36.4 ($CH_2$), 53.1 (CH), 92.9 (C), 126.1 (CH), 126.3 (CH), 128.5 (4×CH), 128.6 (2×CH), 128.7 (2×CH), 128.8 (CH), 132.8 (CH), 141.0 (C), 141.4 (C), 161.1 (C); *m*/*z* (CI) 410 ($MH^+$, 12%), 376 (18), 343 (12), 307 (8), 249 (11), 167 (7), 136 (12), 85 (66), 73 (100); HRMS (CI): $MH^+$, found 410.0847. $C_{21}H_{23}{}^{35}Cl_3NO$ requires 410.0845.

*4.1.16. (4S,5E)-2,2-Dimethyl-4-(trichloromethylcarbonylamino)-8-phenyloct-5-ene (**17**).* The reaction was carried out as described for **15** using (4*E*,6*R*)-2,2-dimethyl-8-phenyloct-4-en-6-ol **12** (0.12 g, 0.53 mmol), 1,8-diazabicyclo[5.4.0]undec-7-ene (0.04 mL, 0.27 mmol) and trichloroacetonitrile (0.08 mL, 0.79 mmol). Purification was carried out by flash column chromatography, and elution with 1:19 ethyl acetate/petroleum ether gave (4*S*,5*E*)-2,2-dimethyl-4-(trichloromethylcarbonylamino)-8-phenyloct-5-ene **17** as a colourless oil (0.19 g, 100%). $R_f$ (20% EtOAc/petroleum ether) 0.59; $\nu_{max}$ (NaCl) 3338 (NH), 2955 (CH), 1689 (CO), 1518, 1245, 822 $cm^{-1}$; $\delta_H$ (400 MHz, $CDCl_3$) 0.95 (9H, s, $C(CH_3)_3$), 1.44 (1H, dd, *J* 14.4, 8.0 Hz, 3-*H*H), 1.53 (1H, dd, *J* 14.4, 4.8 Hz, 3-H*H*), 2.35 (2H, dt, *J* 7.2, 7.0 Hz, 7-$H_2$), 2.68 (2H, t, *J* 7.2 Hz, 8-$H_2$), 4.40–4.49 (1H, m, 4-H), 5.36 (1H, ddt, *J* 15.6, 6.8, 1.2 Hz, 5-H), 5.68 (1H, dtd, *J* 15.2, 7.0, 1.2 Hz, 6-H), 6.41 (1H, d, *J* 8.0 Hz, NH), 7.14–7.29 (5H, m, 5×ArH); $\delta_C$ (100 MHz, $CDCl_3$) 29.9 (3×$CH_3$), 30.5 (C), 34.0 ($CH_2$), 35.4 ($CH_2$), 48.9 ($CH_2$), 50.8 (CH), 92.9 (C), 125.9 (CH), 128.3 (2×CH), 128.5 (2×CH), 130.8 (CH), 131.0 (CH), 141.5 (C), 160.2 (C); *m*/*z* (CI) 376 ($MH^+$, 31%), 342 (49), 306 (100), 272 (43), 215 (10), 168 (36), 107 (57), 71 (49); HRMS (CI): $MH^+$, found 376.1005. $C_{18}H_{25}{}^{35}Cl_3NO$ requires 376.1002.

*4.1.17. (4S,5E)-1-Nitrile-4-(trichloromethylcarbonylamino)-8-phenyloct-5-ene (**18**).* The reaction was carried out as described for **15** using (4*E*,6*R*)-1-nitrile-8-phenyloct-4-en-6-ol **13** (0.18 g, 0.79 mmol), 1,8-diazabicyclo[5.4.0]undec-7-ene (0.06 mL, 0.40 mmol) and trichloroacetonitrile (0.12 mL, 1.19 mmol). Purification was carried out by flash column chromatography, and elution with 1:4 ethyl acetate/petroleum ether gave (4*S*,5*E*)-1-nitrile-4-(trichloromethylcarbonylamino)-8-phenyloct-5-ene **18** as a pale yellow oil (0.24 g, 81%). $R_f$ (20% EtOAc/petroleum ether) 0.24; $\nu_{max}$ (NaCl) 3330 (NH), 2928 (CH), 2250 (CN), 1702 (CO), 1517, 822, 734 $cm^{-1}$; $\delta_H$ (400 MHz, $CDCl_3$) 1.55–1.65 (2H, m, 2-$H_2$), 1.68–1.77 (2H, m, 3-$H_2$), 2.35–2.43 (4H, m, 1-$H_2$ and 7-$H_2$), 2.71 (2H, t, *J* 7.4 Hz, 8-$H_2$), 4.30–4.38 (1H, m, 4-H), 5.33 (1H, ddt, *J* 15.4, 6.8, 1.3 Hz, 5-H), 5.73 (1H, dtd, *J* 15.4, 6.8, 1.0 Hz, 6-H), 6.46 (1H, d, *J* 8.1 Hz, NH), 7.13–7.31 (5H, m, 5×ArH); $\delta_C$ (100 MHz, $CDCl_3$) 16.9 ($CH_2$), 21.7 ($CH_2$), 33.7 ($CH_2$), 33.9 ($CH_2$), 35.2 ($CH_2$), 52.5 (CH), 92.8 (C), 119.2 (C), 126.1 (CH), 128.2 (CH), 128.4 (2×CH), 128.5 (2×CH), 133.7 (CH), 141.1 (C), 161.3 (C); *m*/*z* (CI) 373 ($MH^+$, 22%), 339 (30), 305 (13), 288 (12), 269 (8), 212 (11), 186 (17), 162 (23), 132 (13), 107 (37), 85 (23), 79 (100); HRMS (CI): $MH^+$, found 373.0640. $C_{17}H_{20}{}^{35}Cl_3N_2O$ requires 373.0641.

*4.1.18. (2S,4S,5E)-2-[(tert-Butyldimethylsilyl)oxy]-4-(trichloromethylcarbonylamino)-8-phenyloct-5-ene (**27**).* The reaction was carried out as described for **15** using (4*E*,6*R*)-2-[(*tert*-butyldimethylsilyl)oxy]-8-phenyloct-4-en-6-ol **14** (0.10 g, 0.30 mmol), 1,8-diazabicyclo[5.4.0]undec-7-ene (0.02 mL, 0.15 mmol) and trichloroacetonitrile (0.05 mL, 0.45 mmol). Purification was carried out by flash column chromatography, and elution with 1:19 ethyl acetate/petroleum ether gave (2*S*,4*S*,5*E*)-2-[(*tert*-butyldimethylsilyl)oxy]-4-(trichloromethylcarbonylamino)-8-phenyloct-5-ene **27** as a colourless oil (0.12 g, 87%). $R_f$ (20% EtOAc/petroleum ether) 0.57; $\nu_{max}$ (NaCl) 3337 (NH), 2928 (CH), 1702 (CO), 1514, 1254, 1079, 835, 449 $cm^{-1}$; $[\alpha]_D^{22}$ −12.0 (*c* 0.3, $CHCl_3$); $\delta_H$ (400 MHz, $CDCl_3$) 0.04 (3H, s, $SiCH_3$), 0.05 (3H, s, $SiCH_3$), 0.89 (9H, s, $SiC(CH_3)_3$), 1.18 (3H, d, *J* 6.0 Hz, 1-$H_3$), 1.60–1.68 (1H, m, 3-*H*H), 1.71–1.79 (1H, m, 3-H*H*), 2.37 (2H, q, *J* 7.0 Hz, 7-$H_2$), 2.70 (2H, t, *J* 7.0 Hz, 8-$H_2$), 3.82 (1H, q, *J* 6.0 Hz, 2-H), 4.46 (1H, quin, *J* 6.8 Hz, 4-H), 5.40 (1H, dd, *J* 15.4, 6.8 Hz, 5-H), 5.72 (1H, dt, *J* 15.4, 7.0 Hz, 6-H), 6.52 (1H, d, *J* 8.0 Hz, NH), 7.14–7.30 (5H, m, 5×ArH); $\delta_C$ (100 MHz, $CDCl_3$) −4.6 ($CH_3$), −4.1 ($CH_3$), 18.1 (C), 24.0 ($CH_3$), 25.9 (3×$CH_3$), 34.0 ($CH_2$), 35.4 ($CH_2$), 44.8 ($CH_2$), 50.7 (CH), 65.8 (CH), 92.9 (C), 126.0 (CH), 128.4 (2×CH), 128.5 (2×CH), 129.1 (CH), 132.4 (CH), 141.4 (C), 160.7 (C); *m*/*z* (CI) 480 ($MH^+$, 100%), 444 (75), 410 (19), 352 (14), 318 (5), 159 (11), 133 (8), 81 (4); HRMS (CI): $MH^+$, found 480.1490. $C_{22}H_{35}{}^{35}Cl_2{}^{37}ClNO_2Si$ requires 480.1477.

*4.1.19. Methyl (2S)-2-(trichloromethylcarbonylamino)hexanoate (**19**)*[8h]. To a stirred solution of (5*S*,6*E*)-9-phenyl-5-(trichloromethylcarbonylamino)non-6-ene **15** (0.14 g, 0.39 mmol) in carbon tetrachloride (6.0 mL) and acetonitrile (6.0 mL), sodium metaperiodate (0.34 g, 1.61 mmol, dissolved in water, 9 mL) was added, followed by ruthenium(III) chloride hydrate (0.01 g, 0.04 mmol). The reaction mixture was stirred at room temperature before water (100 mL) and dichloromethane (100 mL) were added. The organic layer was then dried ($MgSO_4$), filtered and concentrated in vacuo to give a dark oil (0.12 g). This residue was then dissolved in methanol (5.0 mL) and the solution cooled to 0 °C before thionyl chloride (0.16 mL, 2.21 mmol) was added dropwise. The reaction mixture was then heated under reflux for 22 h before being concentrated in vacuo. The residue was partitioned between a saturated solution of sodium bicarbonate (30 mL) and ethyl acetate (30 mL) and the organic layer was dried ($MgSO_4$), filtered and concentrated in vacuo. Purification was carried out by flash column chromatography, and elution with 1:9 diethyl ether/petroleum ether gave methyl (2*S*)-2-(trichloromethylcarbonylamino)hexanoate **19** as a colourless oil (0.04 g, 34%). $R_f$ (20% EtOAc/petroleum ether) 0.58; $\delta_H$ (400 MHz, $CDCl_3$) 0.87–0.93 (3H, m, 6-$H_3$), 1.30–1.40 (4H, m, 4-$H_2$ and 5-$H_2$), 1.72–1.83 (1H, m, 3-*H*H), 1.92–2.04 (1H, m, 3-H*H*), 3.81 (3H, s, $OCH_3$), 4.58 (1H, q, *J* 6.2 Hz, 2-H), 7.14 (1H, d, *J* 6.2 Hz, NH); $\delta_C$ (100 MHz, $CDCl_3$) 13.9 ($CH_3$), 22.2 ($CH_2$), 27.0 ($CH_2$), 31.7 ($CH_2$), 52.9 ($CH_3$), 54.0 (CH), 92.2 (C), 161.4 (C), 171.9 (C); *m*/*z* (CI) 290 ($MH^+$, 80%), 256 (100), 222 (20), 179 (10), 127 (5), 85 (40), 69 (55); HRMS (CI): $MH^+$, found 290.0130. $C_9H_{15}{}^{35}Cl_3NO_3$ requires 290.0118.

*4.1.20. Methyl (2S)-4-phenyl-2-(trichloromethylcarbonylamino)butanoate (**20**).* The reaction was carried out as described for **19** using (3*S*,4*E*)-1,7-diphenyl-3-(trichloromethylcarbonylamino)hept-4-ene **16** (0.10 g, 0.24 mmol), sodium metaperiodate (0.21 g, 1.00 mmol, dissolved in water, 9.0 mL) and ruthenium(III) chloride hydrate (0.003 g, 0.01 mmol). Purification was carried out by flash column chromatography, and elution with 1:9 ethyl acetate/petroleum ether gave methyl (2*S*)-4-phenyl-2-(trichloromethylcarbonylamino)butanoate **20** as a colourless oil (0.039 g, 42%). $R_f$ (20% EtOAc/petroleum ether) 0.39; $\nu_{max}$ (NaCl) 3344 (NH), 2925 (CH), 1742 (CO), 1713 (CO), 1513, 1455, 1215, 821 $cm^{-1}$; $\delta_H$ (400 MHz, $CDCl_3$) 2.05–2.14 (1H, m, 3-*H*H), 2.22–2.32 (1H, m, 3-H*H*), 2.55–2.69 (2H, m, 4-$H_2$), 3.71 (3H, s, $OCH_3$), 4.56 (1H, q, *J* 5.2 Hz, 2-H), 7.08–7.25 (5H, m, 5×ArH); $\delta_C$ (100 MHz, $CDCl_3$) 31.3 ($CH_2$), 33.3 ($CH_2$), 52.9 ($CH_3$), 53.7 (CH), 93.6 (C), 126.5 (CH), 128.4 (2×CH), 128.7 (2×CH), 140.0 (C), 161.5 (C), 171.5 (C); *m*/*z* (CI) 338 ($MH^+$, 100%), 304 (45), 270 (4), 233 (4), 117 (3), 69 (12); HRMS (CI): $MH^+$, found 338.0117. $C_{13}H_{15}{}^{35}Cl_3NO_3$ requires 338.0118.

*4.1.21. Methyl (2S)-4,4-dimethyl-2-(trichloromethylcarbonylamino)pentanoate (**21**).* The reaction was carried out as described for **19** using (4*S*,5*E*)-2,2-dimethyl-4-(trichloromethylcarbonylamino)-8-phenyloct-5-ene **17** (0.15 g, 0.40 mmol), sodium metaperiodate

(0.35 g, 1.63 mmol, dissolved in water, 9.0 mL) and ruthenium(III) chloride hydrate (0.008 g, 0.04 mmol). Purification was carried out by flash column chromatography, and elution with 3:17 ethyl acetate/petroleum ether gave methyl (2*S*)-4,4-dimethyl-2-(trichloromethylcarbonylamino)pentanoate **21** as a yellow solid (0.075 g, 62%). Mp 76–79 °C; $R_f$ (20% EtOAc/petroleum ether) 0.41; $\nu_{max}$ (NaCl) 3422 (NH), 2960 (CH), 1743 (CO), 1716 (CO), 1516, 1371, 1215, 908 $cm^{-1}$; $\delta_H$ (400 MHz, $CDCl_3$) 1.00 (9H, s, $C(CH_3)_3$), 1.58–1.70 (1H, m, 3-*H*H), 1.88 (1H, dd, *J* 14.6, 3.1 Hz, 3-H*H*), 3.78 (3H, s, $OCH_3$), 4.62 (1H, td, *J* 8.6, 3.1 Hz, 2-H), 6.94 (1H, br m, NH); $\delta_C$ (100 MHz, $CDCl_3$) 29.5 (3×$CH_3$), 30.7 (C), 45.8 ($CH_2$), 51.8 ($CH_3$), 52.8 (CH), 106.9 (C), 161.4 (C), 172.3 (C); *m*/*z* (CI) 304 ($MH^+$, 100%), 270 (86), 236 (19), 186 (3), 158 (4), 113 (9), 81 (32), 69 (29); HRMS (CI): $MH^+$, found 304.0264. $C_{10}H_{17}{}^{35}Cl_3NO_3$ requires 304.0274.

*4.1.22. Methyl (2S)-5-nitrile-2-(trichloromethylcarbonylamino)pentanoate (**22**).* The reaction was carried out as described for **19** using (4*S*,5*E*)-1-nitrile-4-(trichloromethylcarbonylamino)-8-phenyloct-5-ene **18** (0.12 g, 0.32 mmol), sodium metaperiodate (0.28 g, 1.37 mmol, dissolved in water, 6 mL) and ruthenium(III) chloride hydrate (0.007 g, 0.03 mmol). Purification was carried out by flash column chromatography, and elution with 1:3 ethyl acetate/petroleum ether gave methyl (2*S*)-5-nitrile-2-(trichloromethylcarbonylamino)pentanoate **22** as a pale yellow oil (0.056 g, 58%). $R_f$ (20% EtOAc/petroleum ether) 0.09; $\nu_{max}$ (NaCl) 3339 (NH), 2918 (CH), 2253 (CN), 1744 (CO), 1712 (CO), 1521, 1439, 1217, 912, 735 $cm^{-1}$; $\delta_H$ (400 MHz, $CDCl_3$) 1.65–1.85 (2H, m, 4-$H_2$), 1.88–1.98 (1H, m, 3-*H*H), 2.13–2.23 (1H, m, 3-H*H*), 2.44 (2H, t, *J* 7.0 Hz, 5-$H_2$), 3.85 (3H, s, $OCH_3$), 4.61 (1H, td, *J* 7.5, 6.0 Hz, 2-H), 7.33 (1H, d, *J* 6.0 Hz, NH); $\delta_C$ (100 MHz, $CDCl_3$) 16.8 ($CH_2$), 21.4 ($CH_2$), 31.3 ($CH_2$), 53.1 (CH), 53.3 ($CH_3$), 92.0 (C), 118.8 (C), 161.9 (C), 171.1 (C); *m*/*z* (CI) 301 ($MH^+$, 69%), 267 (76), 251 (10), 233 (48), 199 (9), 183 (9), 155 (12), 113 (25), 107 (85), 71 (100); HRMS (CI): $MH^+$, found 300.9900. $C_9H_{12}{}^{35}Cl_3N_2O_3$ requires 300.9914.

*4.1.23. Methyl (2S,4S)-4-[(tert-butyldimethylsilyl)oxy]-2-(trichloromethylcarbonylamino)pentanoate (**28**).* To a stirred solution of (2*S*,4*S*,5*E*)-2-[(*tert*-butyldimethylsilyl)oxy]-4-(trichloromethylcarbonylamino)-8-phenyloct-5-ene **27** (0.10 g, 0.22 mmol) in *tert*-butanol (2 mL), potassium carbonate (0.09 g, 0.67 mmol) in water (4 mL) was added, followed by sodium metaperiodate (0.14 g, 0.67 mmol) and potassium permanganate (0.03 g, 0.20 mmol). The reaction mixture was stirred at room temperature for 48 h and then further potassium carbonate (0.05 g, 0.34 mmol), sodium metaperiodate (0.07 g, 0.34 mmol) and potassium permanganate (0.02 g, 0.10 mmol) were added. The reaction was stirred at room temperature for a further 40 h and further potassium carbonate (0.03 g, 0.22 mmol), sodium metaperiodate (0.05 g, 0.22 mmol) and potassium permanganate (0.01 g, 0.07 mmol) were added. The reaction was stirred again for 18 h before being filtered through a pad of Celite®, and washed with ethyl acetate (50 mL). Water (50 mL) was added to the filtrate, and the layers were separated. The aqueous layer was extracted further using ethyl acetate (3×50 mL) and the combined organic layers were dried ($MgSO_4$), filtered and concentrated in vacuo to give a yellow oil (0.09 g). This residue was then dissolved in methanol (5 mL) and toluene (5 mL) and (trimethylsilyl) diazomethane solution in diethyl ether (2 M, 2.23 mL, 4.46 mmol) was added dropwise. The reaction was stirred at room temperature for 1.75 h before being concentrated in vacuo. Purification was carried out by flash column chromatography, and elution with 1:9 diethyl ether/petroleum ether gave methyl (2*S*,4*S*)-4-[(*tert*-butyldimethylsilyl)oxy]-2-(trichloromethylcarbonylamino)pentanoate **28** as a colourless oil (0.027 g, 30%). $R_f$ (20% EtOAc/petroleum ether) 0.46; $\nu_{max}$ (NaCl) 3420 (OH), 2858 (CH), 1638 (CO), 1254, 1142, 882 $cm^{-1}$; $[\alpha]_D^{20}$ +25.6 (*c* 0.8, $CHCl_3$); $\delta_H$ (400 MHz, $CDCl_3$) 0.06 (3H, s, $SiCH_3$), 0.07 (3H, s, $SiCH_3$), 0.88 (9H, s, $SiC(CH_3)_3$), 1.20 (3H, d, *J* 6.0 Hz, 5-$H_3$), 1.98–2.08 (1H, m, 3-*H*H), 2.09–2.18 (1H, m, 3-H*H*), 3.79 (3H, s, $OCH_3$), 3.95–4.04 (1H, m, 4-H), 4.57 (1H, apparent q, *J* 5.9 Hz, 2-H), 7.51 (1H, d, *J* 5.9 Hz, NH); $\delta_C$ (100 MHz, $CDCl_3$) −4.5 ($CH_3$), −4.3 ($CH_3$), 18.2 (C), 23.6 ($CH_3$), 26.0 (3×$CH_3$), 40.4 ($CH_2$), 51.8 ($CH_3$), 52.8 (CH), 65.7 (CH), 92.2 (C), 161.5 (C), 171.7 (C); *m*/*z* (CI) 408 ($MH^+$, 25%), 372 (39), 338 (13), 271 (9), 240 (11), 207 (6), 173 (9), 133 (7), 113 (40), 69 (100); HRMS (CI): $MH^+$, found 408.0746. $C_{14}H_{27}{}^{35}Cl_2{}^{37}ClNO_4Si$ requires 408.0748.

*4.1.24. (2S)-2-Aminohexanoic acid (**23**)[27].* (2*S*)-2-(Trichloromethylcarbonylamino)hexanoic acid **19** (0.02 g, 0.08 mmol) was dissolved in 6 M hydrochloric acid (3.0 mL) and the reaction mixture was heated under reflux for 18 h before being washed with diethyl ether (2×20 mL). The aqueous phase was then concentrated in vacuo to give (2*S*)-2-aminohexanoic acid **23** as a pale yellow solid (0.02 g, 98%). $\delta_H$ (400 MHz, $D_2O$) 0.87 (3H, t, *J* 6.8 Hz, 6-$H_3$), 1.30–1.42 (4H, m, 4-$H_2$ and 5-$H_2$), 1.80–2.00 (2H, m, 3-$H_2$), 4.00 (1H, t, *J* 6.0 Hz, 2-H); $\delta_C$ (100 MHz, $D_2O$) 12.9 ($CH_3$), 21.5 ($CH_2$), 26.2 ($CH_2$), 29.4 ($CH_2$), 53.2 (CH), 172.7 (C); *m*/*z* (CI) 132 ($MH^+$, 100%), 113 (13), 97 (13), 81 (23), 71 (22).

*4.1.25. (2S)-2-Amino-4-phenylbutanoic acid (**24**)[28].* Methyl (2*S*)-4-phenyl-2-(trichloromethylcarbonylamino)butanoate **20** (0.02 g, 0.05 mmol) was dissolved in 6 M hydrochloric acid (5.0 mL) and the reaction mixture was heated under reflux for 20 h before water (25 mL) and diethyl ether (30 mL) were added. The aqueous phase was then concentrated in vacuo to give (2*S*)-2-amino-4-phenylbutanoic acid **24** as a yellow solid (0.02 g, 100%). $\delta_H$ (400 MHz, $D_2O$) 2.15–2.36 (2H, m, 2-$H_2$), 2.70–2.88 (2H, m, 1-$H_2$), 4.07 (1H, t, *J* 5.8 Hz, 3-H), 7.27–7.43 (5H, m, 5×ArH); $\delta_C$ (100 MHz, $D_2O$) 30.5 ($CH_2$), 31.9 ($CH_2$), 57.4 (CH), 126.6 (CH), 128.5 (2×CH), 128.9 (2×CH), 140.3 (C), 173.3 (C); *m*/*z* (CI) 180 ($MH^+$, 4%), 161 (22), 137 (56), 113 (31), 97 (33), 81 (73), 69 (100).

*4.1.26. (2S)-2-Amino-4,4-dimethylpentanoic acid (**25**)[29].* Methyl (2*S*)-4,4-dimethyl-2-(trichloromethylcarbonylamino)pentanoate **21** (0.05 g, 0.15 mmol) was dissolved in 6 M hydrochloric acid (5.0 mL) and the resulting solution was heated under reflux for 24 h before water (10 mL) and diethyl ether (20 mL) were added. The aqueous phase was then concentrated in vacuo to give (2*S*)-2-amino-4,4-dimethylpentanoic acid **25** as a pale yellow solid (0.04 g, 100%). $\delta_H$ (400 MHz, $D_2O$) 1.00 (9H, s, $C(CH_3)_3$), 1.70 (1H, dd, *J* 15.0, 5.6 Hz, 3-*H*H), 2.04 (1H, dd, *J* 15.0, 5.6 Hz, 3-H*H*), 4.07 (1H, t, *J* 5.6 Hz, 2-H); $\delta_C$ (100 MHz, $D_2O$) 28.3 (3×$CH_3$), 29.6 (C), 43.8 ($CH_2$), 50.5 (CH), 173.2 (C); *m*/*z* (CI) 146 ($MH^+$, 100%), 135 (6), 113 (10), 97 (13), 81 (26), 69 (32).

*4.1.27. (2S)-2-Amino-5-carbamoylpentanoic acid (**26**)[30].* (2*S*)-5-Nitrile-2-(trichloromethylcarbonylamino)pentanoate **22** (0.03 g, 0.08 mmol) was dissolved in 6 M hydrochloric acid (5.0 mL) and the resulting solution was heated under reflux for 24 h before water (20 mL) and diethyl ether (20 mL) were added. The aqueous phase was then concentrated in vacuo to give (2*S*)-2-amino-5-carbamoylpentanoic acid as an off-white residue (0.02 g, 100%). $\delta_H$ (400 MHz, $D_2O$) 1.60–1.80 (2H, m, 4-$H_2$), 1.85–2.00 (2H, m, 3-$H_2$), 2.46 (2H, t, *J* 7.2 Hz, 5-$H_2$), 3.88 (1H, t, *J* 6.2 Hz, 2-H); $\delta_C$ (100 MHz, $D_2O$) 19.8 ($CH_2$), 29.2 ($CH_2$), 32.9 ($CH_2$), 53.1 (CH), 172.5 (C), 177.7 (C); *m*/*z* (CI) 161 ($MH^+$, 3%), 135 (23), 113 (62), 85 (72), 71 (90).

*4.1.28. (2S,4S)-4-Hydroxy-2-aminopentanoic acid (**29**)[20].* (2*S*,4*S*)-4-[(*tert*-Butyldimethylsilyl)oxy]-2-(trichloromethylcarbonylamino) pentanoate **28** (0.03 g, 0.06 mmol) was dissolved in 6 M hydrochloric acid (4.0 mL) and the resulting solution was heated under reflux for 16 h before water (20 mL) and diethyl ether (20 mL) were added. The aqueous phase was then concentrated in vacuo to give (2*S*,4*S*)-4-hydroxy-2-aminopentanoic acid as a pale brown solid

(0.02 g, 100%). $[\alpha]_D^{20}$ +18.6 (*c* 0.2, $H_2O$), lit.[20] $[\alpha]_D^{20}$ +21.0 (*c* 1.3, $H_2O$); $\delta_H$ (400 MHz, $D_2O$) 1.27 (3H, d, *J* 6.6 Hz, 5-$H_3$), 1.76–1.84 (1H, m, 3-*H*H), 2.09–2.15 (1H, m, 3-H*H*), 3.82 (1H, dd, *J* 9.4, 4.4 Hz, 2-H), 4.08–4.12 (1H, m, 4-H); $\delta_C$ (100 MHz, $D_2O$) 22.7 ($CH_3$), 38.6 ($CH_2$), 54.2 (CH), 66.7 (CH), 174.7 (C); *m*/*z* (CI) 134 ($MH^+$, 5%), 116 (100), 97 (13), 71 (23).

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## Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2010.05.066.

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