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Studies on the aza-Claisen rearrangement of 4,5-dihydroxylated allylic trichloroacetimidates: the stereoselective synthesis of (2*R*,3*S*)- and (2*S*,3*S*)-2-amino-3,4-dihydroxybutyric acids

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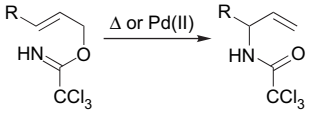
ABSTRACT

Two new synthetic approaches, involving substrate directed aza-Claisen rearrangements and aza-Claisen rearrangements mediated by chiral Pd(II) catalysts, have been developed for the stereoselective synthesis of (2*R*,3*S*)-2-amino-3,4-dihydroxybutyric acid, a dihydroxylated α-amino acid from the edible mushroom, *Lyophyllum ulmarium* and its (2*S*,3*S*)-unnatural diastereomer.

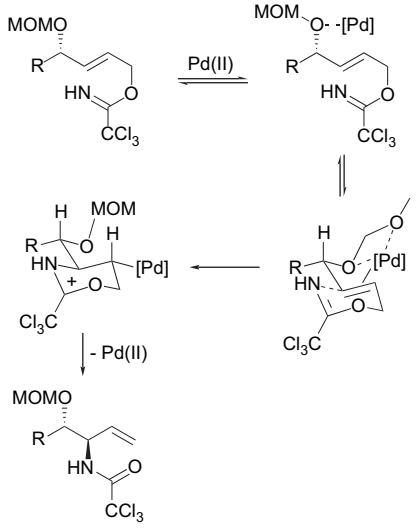
1. Introduction

The aza-Claisen rearrangement of allylic trichloroacetimidates (Scheme 1), commonly known as the Overman rearrangement, has found widespread application for the total synthesis of nitrogen-containing natural products.[1] This is due to the mild conditions employed for this transformation as well as the excellent transfer of chirality during the rearrangement via well-defined chair-like transition states.[1,2] This is particularly the case for the metal-catalysed reaction, where understanding of the cyclisation-induced rearrangement mechanism has lead to the development of highly effective chiral Pd(II) catalysts, which give the allylic trichloroacetamides in high yields and in excellent enantioselectivity.[3]



Scheme 1. Rearrangement of allylic trichloroacetimidates.

In our research, we initiated a programme to study how the Overman rearrangement can be influenced by stereogenic centres within the molecule.[4] Extensive experimentation revealed that the presence of an adjacent MOM-ether results in a highly effective directed rearrangement giving *erythro* products in diastereomeric ratios of up to 16:1.[5] More recently, a series of substrates were prepared to investigate the influence of this directing effect and this showed that both oxygen atoms from the MOM group are required for a highly diastereoselective process (Scheme 2).[6] The products of



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

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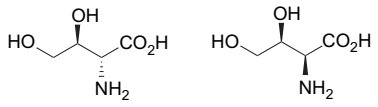
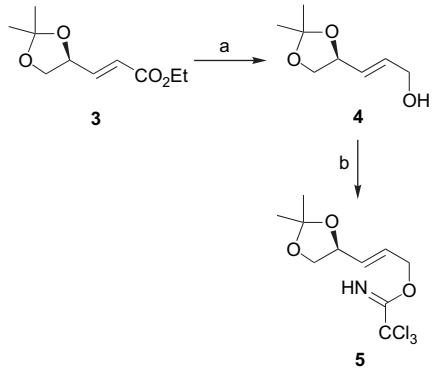
the MOM-ether directed rearrangements are excellent synthetic intermediates and have been oxidised to give β-hydroxy-α-amino acids or used in combination with ring closing metathesis (RCM) reactions for the synthesis of piperidine natural products.[7]

In an effort to extend the scope of this process for highly functionalised α-amino acids, we recently reported the stereoselective synthesis of (2*R*,3*S*)-2-amino-3,4-dihydroxybutyric acid **1**, a dihydroxylated α-amino acid from the edible mushroom, *Lyophyllum ulmarium*, using the MOM-ether directed rearrangement.[8] We now report a new five-step synthesis of (2*S*,3*S*)-2-amino-3,4-dihydroxybutyric acid **2**, which involves a matched substrate–catalyst pairing to effect a highly diastereoselective aza-Claisen rearrangement. We also report in full the synthesis of (2*R*,3*S*)-2-amino-3,4-dihydroxybutyric acid **1** using the MOM-ether directed rearrangement as well as new results, which show that an *erythro*-allylic tri-chloroacetamide can be generated in high diastereoselectivity using a mismatched substrate–catalyst pairing.



2. Results and discussion

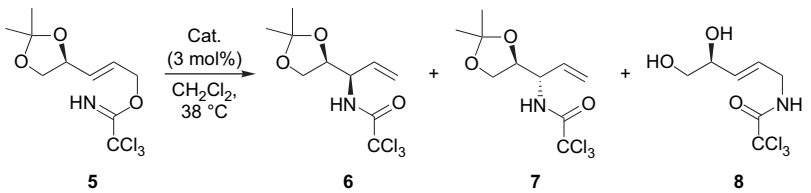
Our strategy for the preparation of amino acids **1** and **2** was to synthesise a protected 4,5-dihydroxylated allylic alcohol and then use an Overman rearrangement to create the key allylic trichloroacetamide, which could then be oxidised and deprotected to give the desired targets. Thus, commercially available ethyl (2*E*,4*S*)-4,5-*O*-isopropylidene-4,5-dihydroxypenten-2-oate **3** was reduced with DIBAL-H to give the corresponding allylic alcohol **4** in 94% yield (Scheme 3). This was then treated with trichloroacetonitrile and DBU to give allylic trichloroacetimidate **5**, which was used in all rearrangement reactions without further purification.



Scheme 3. Reagents and conditions: (a) DIBAL-H (2.2 equiv), Et_2O, −78 °C to rt, 94%; (b) Cl_3CCN, DBU, CH_2Cl_2.

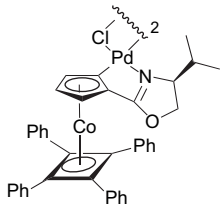
Although MOM-ethers are the most effective at directing the Overman rearrangement, it was proposed that the acetonide protected allylic trichoroacetimidate **5** would still undergo a directed rearrangement using the oxygen atom at the 4-position. Therefore, **5** was treated with bis(acetonitrile)palladium(II) chloride under standard conditions (Table 1, entry 1). This gave the two diastereomeric allylic trichloroacetamides **6** and **7** in 36% yield and in a 1:7 ratio. The low yield of **6** and **7** is due to a competing pathway involving Pd(II)-catalysed hydrolysis of the acetonide followed by 1,3-rearrangement of the allylic trichloroacetimidate by a non-concerted ionisation pathway resulting in the formation of allylic trichloroacetamide **8**.[7a,9] While Pd(II)-mediated hydrolysis reactions of acetals and ketals are known in aqueous acetonitrile, it was surprising to observe this process occurring in anhydrous dichloromethane.[10] Rearrangement of **5** was also done using other metal catalysts known to effect the Overman rearrangement such as Pt(II), Au(I) and Au(III).[5b,11] Unfortunately, these reactions yielded similar results as described for the Pd(II)-catalysed rearrangement. As these metal complexes all acted as Lewis acids, resulting in hydrolysis of the acetonide, it was proposed that a bulky, sterically hindered metal complex would be unable to effectively deprotect the 1,2-diol, leading to higher yields of the desired allylic trichloroacetamides **6** and **7**. Overman and co-workers have developed chiral palladium(II) catalysts such as (*S*)-COP-Cl **9**, which catalyse the rearrangement of allylic trichloroacetimidates in high yields and excellent enantioselectivities.[3e,f,k] It was reasoned that the use of such chiral catalysts would not only prevent hydrolysis of the acetonide but also give an enhancement in diastereoselectivity. In the event, treatment of allylic trichloroacetimidate **5** with (*S*)-COP-Cl **9** gave allylic trichloroacetamides **6** and **7** in 81% yield and in an excellent 52:1 ratio (96% de, entry 2). (*S*)-COP-Cl is known to give allylic trichloroacetamides with the same absolute configuration as C-3 of **6**, resulting from the catalyst complexing to the back face of the allylic trichloroacetimidate. The stereocentre already present in allylic trichloroacetimidate **5** prevents attack for the front face. Thus, this is an example of a matched pairing between substrate and catalyst, and this double stereodifferenation leads to an enhanced diastereoselective outcome for this reaction. To confirm this, allylic trichloroacetimidate **5** was treated with (*R*)-COP-Cl and as expected, this mismatched pairing results in a significantly slower reaction giving allylic trichloroacetamide **7** as the major diastereomer in only a 6:1 ratio. Furthermore, significant quantities of allylic trichloroacetamide **8** were also isolated, showing that deprotection of the 1,2-diol by (*R*)-COP-Cl is just as facile than complexing to the more hindered front face of the alkene to effect the Overman rearrangement.

Table 1



Entry	Catalyst	Reaction time (h)	Yield[a] (%)	Ratio[b] (**6**/**7**/**8**)
1[c]	$PdCl_2(MeCN)_2$	24	36	1:7:7
2	(*S*)-COP-Cl	168	81	52:1:0
3	(*R*)-COP-Cl	336	23	1:6:5

[a] Isolated combined yields of **6** and **7** from *E*-allylic alcohol **4**.
[b] Ratio in crude reaction mixture.
[c] Catalyst loading: 10 mol %.



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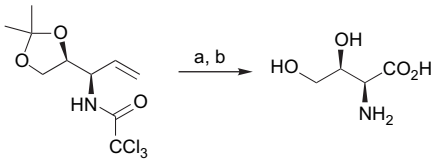
With sufficient quantities of *threo*-diastereomer **6** available via the highly selective (*S*)-COP-Cl catalysed rearrangement, the stereoselective synthesis of (2*S*,3*S*)-2-amino-3,4-dihydroxybutyric acid **2** was completed. Oxidation of allylic trichloroacetamide **6** with catalytic ruthenium(III) trichloride hydrate and sodium metaperiodate gave the corresponding carboxylic acid (Scheme 4).[12] Deprotection of the amino and 1,2-diol functional groups was then carried out using 6 M hydrochloric acid, which gave amino acid **2** in 47% yield over the two steps.

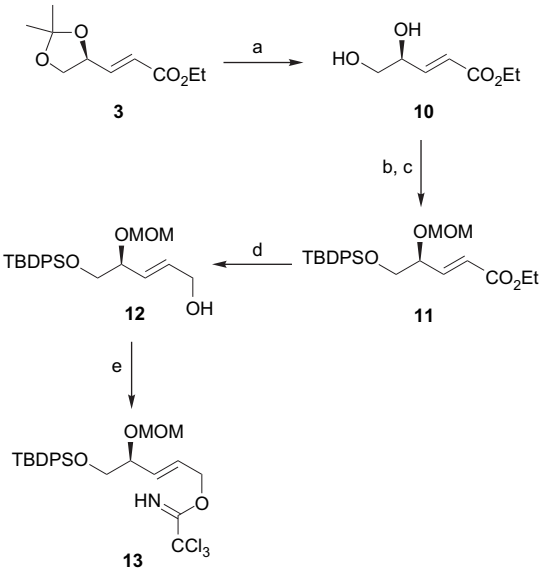


6 2

Scheme 4. Reagents and conditions: (a) $RuCl_3 \cdot xH_2O$, $NaIO_4$, CCl_4, MeCN, H_2O; (b) 6 M HCl, Δ, 47% over two steps.

Although rearrangement of allylic trichloroacetimidate **5** did allow access to allylic trichloroacetamide **6** for the synthesis of (2*S*,3*S*)-2-amino-3,4-dihydroxybutyric acid **2**, the labile nature of the acetonide protecting group prevented efficient synthesis of the *erythro*-diastereomer using the directed rearrangement. To overcome this, the acetonide group was replaced with protecting groups known to be stable to the reaction conditions of metal-catalysed rearrangements.[5–7] Thus, acid hydrolysis of commercially available acetonide **3** gave 1,2-diol **10** in 94% yield (Scheme 5). The primary hydroxyl was protected as the *tert*-butyldiphenylsilyl ether, followed by protection of the secondary hydroxyl as the MOM-ether, which gave **11** in 86% yield over the two steps. It should be noted that the MOM-ether was selected to protect the 4-hydroxyl as MOM-ethers are the most effective at directing the Overman rearrangement. Ester **11** was then reduced using DIBAL-H in good yield and the resulting allylic alcohol **12** was converted to the corresponding allylic trichloroacetimidate **13** using trichloroacetonitrile and DBU.

Allylic trichloroacetimidate **13** was rearranged using the standard metal catalysts for this reaction (Table 2, entries 1–4). As expected, only the two diastereomeric 3,3-products **14** and **15** were isolated from these reactions, indicating the stability of the silyl and MOM-ethers to the reaction conditions. Rearrangement of **13** using platinum(II) chloride, hydrogen tetrachloroaurate(III) hydrate or gold(I) chloride gave **14** and **15** in modest yields and diastereomeric ratios. The best results were obtained using bis(acetonitrile)palladium(II) chloride as the catalyst, which gave after only 12 h, a 68% yield of **14** and **15** (over two steps) and in a 1:4 ratio (entry 4). Our studies on the origin of the MOM-ether directing effect during these rearrangements have shown that to obtain high diastereoselectivities (>10:1), both oxygen atoms are required to participate, while the availability of only the oxygen at the



Scheme 5. Reagents and conditions: (a) 2 M HCl, 94%; (b) TBDPSCl, imidazole, THF, 100%; (c) MOMBr, EtN(*i*-Pr)$_2$, CH_2Cl_2, 86%; (d) DIBAL-H (2.2 equiv), Et_2O, −78 °C to rt, 86%; (e) Cl_3CCN, DBU, CH_2Cl_2.

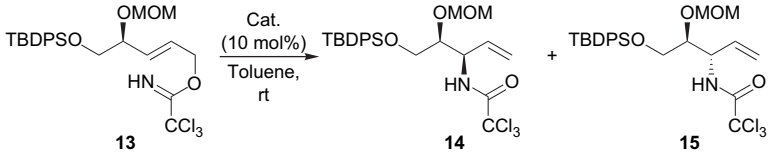
4-position normally produces modest diastereoselectivities (~5:1).[6] Thus, the 4:1 ratio of diastereomers generated from the Pd(II)-catalysed rearrangement of **13** suggests that the presence of the bulky *tert*-butyldiphenylsilyl ether prevents effective co-ordination of both MOM-ether oxygen atoms to the catalyst and that only the adjacent 4-oxygen atom can participate, resulting in the observed diastereoselectivity. Nevertheless, the use of Pd(II) catalyst does allow rapid access to the *erythro*-diastereomer in good yield. It should be noted that the rearrangement of **13** was also carried out using (*R*)-COP-Cl, which gave **14** and **15** in 68% yield and in a 1:16 ratio (entry 5). While this is a mismatched pairing between substrate and catalyst resulting in a slow reaction, the chiral catalyst is still able to induce an asymmetric reaction generating **14** and **15** in high diastereoselectivity (88% de).

To complete the synthesis of (2*R*,3*S*)-2-amino-3,4-dihydroxybutyric acid **1**, allylic trichloroacetamide **15** was oxidised to the corresponding carboxylic acid **16** in 71% yield using the Sharpless protocol (Scheme 6).[12] Deprotection of **16** was then achieved in a two-step protocol involving TBAF removal of the silyl ether. Acid-mediated hydrolysis of the MOM and trichloroacetamide groups then gave natural product **1**, in 44% yield over the two steps.

3. Conclusion

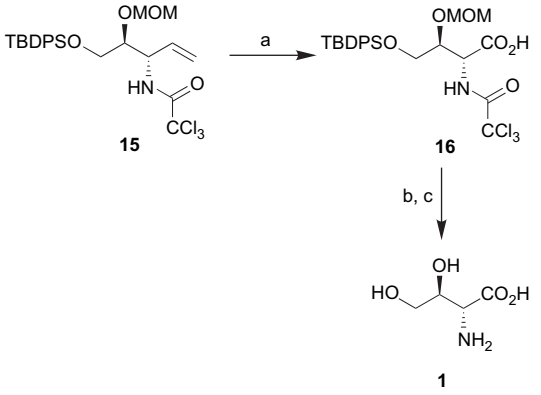
In summary, our studies on the rearrangement of 4,5-dihydroxylated allylic trichloroacetimidates have led to the development of a five-step synthesis of (2*S*,3*S*)-2-amino-3,4-dihydroxybutyric acid **2**, which utilises a commercially available chiral Pd(II) catalyst, (*S*)-COP-Cl, to effect a highly diastereoselective rearrangement giving the *threo*-product in 96% de. Problems associated with transition metal-catalysed hydrolysis of the acetonide protecting group were overcome by synthesising a new allylic trichloroacetimidate bearing silyl ether and MOM-ether protecting groups. Directed rearrangement using bis(acetonitrile)palladium(II) chloride led to a fast, highly efficient reaction, giving the diastereomeric products in 68% yield and in a 4:1 ratio. The diastereomeric outcome could be enhanced using (*R*)-COP-Cl, and while this is a mismatched pairing, this reaction still generated the products in an excellent 16:1 ratio. Oxidation and deprotection then completed the synthesis of (2*R*,3*S*)-2-amino-3,4-dihydroxybutyric acid **1** from *L. ulmarium*. Further studies utilising

Table 2



Entry	Catalyst	Reaction time (h)	Yield[a] (%)	Ratio[b] (**14**/**15**)
1	$PtCl_2$	168	25	1:4
2	$HAuCl_4 \cdot 3H_2O$	48	49	1:2
3	AuCl	168	40	1:3
4	$PdCl_2(MeCN)_2$	12	68	1:4
5[c]	(*R*)-COP-Cl	336	68	1:16

[a] Isolated combined yields of **14** and **15** from *E*-allylic alcohol **12**.
[b] Ratio in crude reaction mixture.
[c] Reaction carried out in CH_2Cl_2 at 38 °C.



Scheme 6. Reagents and conditions: (a) $RuCl_3 \cdot xH_2O$, $NaIO_4$, CCl_4, MeCN, H_2O, 71%; (b) TBAF, THF; (c) 6 M HCl, Δ, 44% over two steps.

4,5-dihydroxylated allylic trichloroacetamides for natural product synthesis is currently underway.

4. Experimental

4.1. General methods

All reactions were performed under a nitrogen atmosphere unless otherwise noted. Reagents and starting materials were obtained from commercial sources and used as-received. Brine refers to a saturated solution of sodium chloride. Flash column chromatography was carried out using Fisher Matrex silica 60. Macherey–Nagel aluminium backed plates pre-coated with silica gel 60 (UV_{254}) were used for thin layer chromatography and were visualised by staining with $KMnO_4$. ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker DPX 400 spectrometer with chemical shift values in parts per million relative to residual chloroform (δ_H 7.28 and δ_C 77.2) as standard. Infrared spectra were recorded using Golden Gate apparatus on a JASCO FTIR 410 spectrometer and mass spectra were obtained using a JEOL JMS-700 spectrometer. Optical rotations were determined as solutions irradiating with the sodium D line (λ=589 nm) using an AA series Automatic polarimeter. $[\alpha]_D$ values are given in units 10^{-1} deg cm^2 g^{-1}.

4.1.1. (2*E*,4*S*)-4,5-(*O*-Isopropylidene)-4,5-dihydroxyprop-2-en-1-ol **4**[13]

Ethyl (2*E*,4*S*)-4,5-(*O*-isopropylidene)-4,5-dihydroxypenten-2-oate **3** (0.5 g, 2.5 mmol) was dissolved in diethyl ether (30 mL) and cooled with stirring under a nitrogen atmosphere to −78 °C. DIBAL-H (1.0 M in hexanes) (5.5 mL, 5.5 mmol) was then added dropwise to the reaction mixture. The reaction mixture was then allowed to warm to room temperature and stirred overnight. The solution was then filtered through a pad of Celite® and washed with diethyl ether (50 mL). Concentration in vacuo then yielded the crude product as a clear oil, which was purified by flash column chromatography (20% diethyl ether/petroleum ether), which gave (2*E*,4*S*)-4,5-(*O*-isopropylidene)-4,5-dihydroxyprop-2-en-1-ol **4** as a colourless oil (0.37 g, 94%). $[\alpha]_D^{25}$ +33.7 (*c* 1.0, $CHCl_3$) (lit.[13] $[\alpha]_D^{24}$ +33.9 (*c* 3.6, $CHCl_3$)); δ_H (400 MHz, $CDCl_3$) 1.40 (3H, s, CH_3), 1.43 (3H, s, CH_3), 3.61 (1H, br t, *J* 8.1 Hz, 5-*H*H), 4.10 (1H, dd, *J* 8.1, 7.0 Hz, 5-H*H*), 4.16 (2H, d, *J* 5.0 Hz, 1-H_2), 4.54 (1H, dt, *J* 14.1, 7.0 Hz, 4-H), 5.72 (1H, dd, *J* 15.5, 7.0 Hz, 3-H), 5.95 (1H, dt, *J* 15.5, 5.0 Hz, 2-H); δ_C (100 MHz, $CDCl_3$) 25.9 (CH_3), 26.7 (CH_3), 62.5 (CH_2), 69.4 (CH_2), 76.5 (CH), 109.4 (C), 128.3 (CH), 133.2 (CH); *m*/*z* (CI) 159 (MH^+, 100%), 141 (27), 83 (49).

4.1.2. Synthesis of allylic trichloroacetimidate **5**

(2*E*,4*S*)-4,5-(*O*-Isopropylidene)-4,5-dihydroxyprop-2-en-1-ol **4** (0.2 g, 1.3 mmol) was dissolved in dichloromethane (20 mL) and cooled to 0 °C under a nitrogen atmosphere. 1,8-Diazabicyclo[5.4.0]undec-7-ene (0.2 mL, 1.5 mmol) and trichloroacetonitrile (0.2 mL, 1.9 mmol) were then added, and the mixture was allowed to warm to room temperature and then stirred for 2 h. The reaction mixture was then filtered through a short pad of silica gel, which was then washed with diethyl ether (75 mL). Concentration in vacuo yielded the product as a brown oil (0.44 g), which was then immediately carried forward to the rearrangement reaction without further purification. δ_H (400 MHz, $CDCl_3$), 1.40 (3H, s, CH_3), 1.45 (3H, s, CH_3), 3.63 (1H, t, *J* 7.7 Hz, 5-*H*H), 4.14 (1H, dd, *J* 11.5, 7.7 Hz, 5-H*H*), 4.57 (1H, q, *J* 7.7 Hz, 4-H), 4.81 (2H, d, *J* 7.5 Hz, 1-H_2), 5.87 (1H, ddt, *J* 15.5, 7.7, 1.2 Hz, 3-H), 6.01 (1H, dt, *J* 15.5, 7.5 Hz, 2-H), 8.36 (1H, br s, NH).

4.1.3. Rearrangement of **5** using $PdCl_2(MeCN)_2$

Allylic trichloroacetimidate **5** (0.38 g, 1.25 mmol) was dissolved in dichloromethane (10 mL) under a nitrogen atmosphere. Bis-(acetonitrile)palladium(II) chloride (0.03 g, 0.1 mmol) was then added and the reaction mixture was stirred at 38 °C for 24 h. The mixture was then filtered through a short pad of Celite® and washed with diethyl ether (40 mL). Concentration under vacuum gave a viscous oil. Purification by flash column chromatography (elution with 10% diethyl ether/petroleum ether) yielded (3*R*,4*S*)-4,5-(*O*-isopropylidene)-3-(trichloromethylcarbonylamino)-4,5-dihydroxypenta-1-ene **6** and then (3*S*,4*S*)-4,5-(*O*-isopropylidene)-3-(trichloromethylcarbonylamino)-4,5-dihydroxypenta-1-ene **7** as colourless oil (0.14 g, 36% combined yield, 1:7 ratio). Further elution (90% diethyl ether/petroleum ether) then yielded (2*E*,4*S*)-1-(trichloromethylcarbonylamino)-4,5-dihydroxypent-2-ene **8** as a colourless oil (0.11 g, 32%). *Data for* **6**: ν_{max}/cm^{-1} (neat) 3418 (NH), 2988 (CH), 1719 (CO), 1506 (C=C), 1373, 1217, 1068; $[\alpha]_D^{23}$ +34.4

(c 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.30 (3H, s, CH_3), 1.41 (3H, s, CH_3), 3.64 (1H, dd, J 8.6, 6.5 Hz, 5-*H*H), 4.04 (1H, dd, J 8.6, 6.5 Hz, 5-H*H*), 4.28 (1H, td, J 6.5, 2.4 Hz, 4-H), 4.41–4.46 (1H, m, 3-H), 5.22–5.31 (2H, m, 1-H_2), 5.81 (1H, ddd, J 17.1, 10.5, 5.7 Hz, 2-H), 6.99 (1H, br d, J 6.9 Hz, NH); δ_C (100 MHz, $CDCl_3$) 24.7 (CH_3), 26.4 (CH_3), 53.9 (CH), 66.4 (CH_2), 76.6 (CH), 92.6 (C), 110.0 (C), 117.7 (CH_2), 133.9 (CH), 162.0 (C); found (CI): 306.0055, $C_{10}H_{15}O_3N^{35}Cl^{37}Cl_2$ requires MH^+ 306.0062. *Data for* **7**: ν_{max}/cm^{-1} (neat) 3418 (NH), 2988 (CH), 1719 (CO), 1506 (C=C), 1373, 1217, 1068; δ_H (400 MHz, $CDCl_3$) 1.28 (3H, s, C*H*$_3$), 1.39 (3H, s, CH_3), 3.78 (1H, dd, J 9.1, 5.0 Hz, 5-*H*H), 4.02 (1H, dd, J 9.1, 6.3 Hz, 5-H*H*), 4.22–4.27 (1H, m, 4-H), 4.40–4.46 (1H, m, 3-H), 5.25–5.32 (2H, m, 1-H_2), 5.78 (1H, ddd, J 16.7, 10.3, 6.2 Hz, 2-H), 6.98 (1H, br d, J 6.9 Hz, NH); δ_C (100 MHz, $CDCl_3$) 24.7 (CH_3), 26.1 (CH_3), 55.8 (CH), 65.5 (CH_2), 76.1 (CH), 92.5 (C), 110.2 (C), 117.7 (CH_2), 131.6 (CH), 161.5 (C); found (CI): 306.0055, $C_{10}H_{15}O_3N^{35}Cl^{37}Cl_2$ requires MH^+ 306.0062; *Data for* **8**: $[\alpha]_D^{25}$ +1.5 (c 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.00 (2H, br s, OH), 4.20 (2H, dd, J 5.0, 1.8 Hz, 1-H_2), 4.36 (1H, t, J 8.0 Hz, 5-*H*H), 4.78 (1H, dd, J 9.8, 8.0 Hz, 5-H*H*), 4.92 (1H, q, J 8.0 Hz, 4-H), 5.77 (1H, ddt, J 15.5, 8.0, 1.6 Hz, 3-H), 5.95 (1H, dt, J 15.5, 5.0 Hz, 2-H); δ_C (100 MHz, $CDCl_3$) 62.6 (CH_2), 67.9 (CH_2), 76.1 (CH), 86.3 (C), 128.2 (CH), 133.3 (CH), 163.3 (C); found (CI): 261.9726, $C_7H_{11}NO_3{}^{35}Cl_3$ requires MH^+ 261.9729.

4.1.4. *Rearrangement of* ***5*** *using (S)-COP-Cl*

Synthesis of allylic trichloroacetimidate **5** and subsequent rearrangement was carried out as described above using (2*E*,4*S*)-4,5-(*O*-isopropylidene)-4,5-dihydroxyprop-2-en-1-ol **4** (1.0 g, 6.3 mmol) and (*S*)-COP-Cl (0.2 g, 3 mol %). The reaction mixture was stirred at 38 °C for 168 h. Purification by flash column chromatography (elution with 10% diethyl ether/petroleum ether) yielded **6** and then **7** as colourless oil (1.55 g, 81% combined yield, 52:1 ratio). Spectroscopic data as described above.

4.1.5. *Rearrangement of* ***5*** *using (R)-COP-Cl*

Synthesis of allylic trichloroacetimidate **5** and subsequent rearrangement was carried out as described above using (2*E*,4*S*)-4,5-(*O*-isopropylidene)-4,5-dihydroxyprop-2-en-1-ol **4** (0.1 g, 0.63 mmol) and (*R*)-COP-Cl (0.03 g, 3 mol %). The reaction mixture was stirred at 38 °C for 336 h. Purification by flash column chromatography (elution with 10% diethyl ether/petroleum ether) yielded **6** and then **7** as colourless oil (0.044 g, 23% combined yield, 1:6 ratio). Further elution (90% diethyl ether/petroleum ether) then yielded **8** as a colourless oil (0.027 g, 16%). Spectroscopic data as described above.

4.1.6. *(2S,3S)-2-Amino-3,4-dihydroxybutyric acid* ***2***[14]

(3*R*,4*S*)-4,5-(*O*-Isopropylidene)-3-(trichloromethylcarbonylamino)-4,5-dihydroxypenta-1-ene **6** (0.5 g, 1.7 mmol) was dissolved in tetrachloromethane (14 mL) and acetonitrile (14 mL). Sodium periodate (1.46 g, 6.8 mmol) in water (22 mL) was added to the solution. Ruthenium trichloride hydrate (18 mg, 0.08 mmol) was added to the biphasic solution and the reaction mixture was then stirred vigorously at room temperature overnight. The reaction mixture was extracted with dichloromethane (4×50 mL), dried ($MgSO_4$) and concentrated in vacuo to yield the crude product as a brown oil (0.25 g). The brown oil (0.25 g) was dissolved in 6 M hydrochloric acid (10 mL) and heated under reflux overnight. The reaction mixture was cooled to room temperature and then extracted with diethyl ether (10 mL). The aqueous phase was then concentrated in vacuo to give the crude product. Purification by ion exchange chromatography (elution with 0.5 M NH_4OH solution) yielded (2*S*,3*S*)-2-amino-3,4-dihydroxybutyric acid **2** as a white solid (0.104 g, 47% over two steps). $[\alpha]_D^{24}$ −9.6 (c 1.0, H_2O) (lit.[14] $[\alpha]_D^{26}$ −10.0 (c 1.0, H_2O)); δ_H (400 MHz, D_2O) 3.61 (2H, t, J 5.2 Hz, 4-H_2), 3.67 (1H, d, J 4.0 Hz, 2-H), 4.03–4.08 (1H, m, 2-H); δ_C (100 MHz, D_2O) 56.7 (CH), 63.3 (CH_2), 69.3 (CH), 172.7 (C); m/z (CI) 136 (MH^+), 91 (30%), 83 (100), 69 (76).

4.1.7. *Ethyl (2E,4S)-4,5-dihydroxypent-2-enoate* ***10***[15]

Ethyl (2*E*,4*S*)-4,5-(*O*-isopropylidene)-4,5-dihydroxy-2-pentenoate **3** (2.0 g, 10 mmol) was dissolved in ethanol (20 mL). Hydrochloric acid (2 M, 10 mL) was then added and the solution was stirred at room temperature for 3 h. The reaction was quenched by the addition of small lumps of sodium hydrogen carbonate (6.0 g). Insoluble material was then removed by filtration and the mixture was concentrated in vacuo. Further insoluble material was removed by filtration and the solution was dried over $MgSO_4$. Purification by filtration through a pad of silica gel gave after concentration, ethyl (2*E*,4*S*)-4,5-dihydroxypent-2-enoate **10** as a clear oil (1.51 g, 94%). $[\alpha]_D^{25}$ −5.0 (c 0.5, $CHCl_3$) (lit.[15] $[\alpha]_D^{25}$ −5.5 (c 1.6, $CHCl_3$)); δ_H (400 MHz, $CDCl_3$) 1.29 (3H, t, J 7.1 Hz, OCH_2CH_3), 2.61 (2H, br s, 2×OH), 3.53 (1H, dd, J 11.5, 7.1 Hz, 5-*H*H), 3.74 (1H, dd, J 11.5, 3.4 Hz, 5-H*H*), 4.19 (2H, q, J 7.1 Hz, OCH_2CH_3), 4.39–4.45 (1H, m, 4-H), 6.13 (1H, dd, J 15.7, 1.8 Hz, 2-H), 6.90 (1H, dd, J 15.7, 4.4 Hz, 3-H); δ_C (100 MHz, $CDCl_3$) 14.2 (CH_3), 60.8 (CH_2), 65.6 (CH_2), 71.7 (CH), 121.9 (CH), 146.3 (CH), 166.7 (C); m/z (CI) 161 (MH^+, 100%), 99 (57), 75 (30).

4.1.8. *Ethyl (2E,4S)-5-(tert-butyldiphenylsilyloxy)-4-hydroxypent-2-enoate*[16]

Ethyl (2*E*,4*S*)-4,5-dihydroxypent-2-enoate **10** (1.0 g, 6.3 mmol) was dissolved in THF (40 mL) under a nitrogen atmosphere. *tert*-Butyldiphenylchlorosilane (2.4 g, 8.7 mmol) and imidazole (0.9 g, 12.5 mmol) were then added, and the solution was stirred at room temperature overnight. The solution was then diluted with ethyl acetate (50 mL) and washed with water (50 mL). The organic extracts were dried ($MgSO_4$) and concentrated in vacuo. Flash column chromatography (elution with 10% diethyl ether/petroleum ether) yielded the title compound, ethyl (2*E*,4*S*)-5-(*tert*-butyldiphenylsilyloxy)-4-hydroxypent-2-enoate, as a clear oil (2.48 g, 100%). $[\alpha]_D^{25}$ −17.8 (c 1.6, $CHCl_3$) (lit.[16] $[\alpha]_D^{22}$ −16.4 (c 0.2, $CHCl_3$)); δ_H (400 MHz, $CDCl_3$) 1.08 (9H, s, *t*-Bu), 1.27 (3H, t, J 7.2 Hz, OCH_2CH_3), 2.74 (1H, br d, J 4.2 Hz, 4-OH), 3.55 (1H, dd, J 10.2, 4.0 Hz, 5-*H*H), 3.76 (1H, dd J 10.2, 2.1 Hz, 5-H*H*), 4.19 (2H, q, J 7.2 Hz, OCH_2CH_3), 4.38–4.42 (1H, m, 4-H), 6.14 (1H, dd, J 15.7, 2.2 Hz, 2-H), 6.80 (1H, dd, J 15.7, 4.3 Hz, 3-H), 7.37–7.47 (6H, m, Ar–H), 7.62–7.68 (4H, m, Ar–H); δ_C (100 MHz, $CDCl_3$) 14.3 (CH_3), 19.3 (C), 26.9 (CH_3), 60.5 (CH_2), 67.0 (CH_2), 71.5 (CH), 122.0 (CH), 127.9 (CH), 130.0 (CH), 132.8 (C), 135.6 (CH), 145.8 (CH), 166.3 (C); m/z (CI) 381 (MH^+−OH, 14%), 321 (100), 257 (5), 217 (4), 143 (8).

4.1.9. *Ethyl (2E,4S)-5-(tert-butyldiphenylsilyloxy)-4-(methoxymethoxy)pent-2-enoate* ***11***[16]

Ethyl (2*E*,4*S*)-5-(*tert*-butyldiphenylsilyloxy)-4-hydroxypent-2-enoate (0.1 g, 0.25 mmol) was dissolved in dichloromethane (20 mL) and cooled to 0 °C under a nitrogen atmosphere. Chloromethylmethyl ether (0.1 mL, 1.25 mmol) was added dropwise and the solution was stirred for 0.5 h. *N*,*N*-Diisopropylethylamine (0.2 mL, 1.25 mmol) was added dropwise and the solution was then heated under reflux overnight. The solution was diluted with dichloromethane (20 mL) and washed with water (20 mL), and then acidified with 2 M hydrochloric acid solution (10 mL). The organic extracts were then dried ($MgSO_4$) and the filtrate concentrated in vacuo. Flash column chromatography (20% diethyl ether/petroleum ether) yielded ethyl (2*E*,4*S*)-5-(*tert*-butyldiphenylsilyloxy)-4-(methoxymethoxy)pent-2-enoate **11** as a colourless oil (0.13 g, 86%). $[\alpha]_D^{25}$ +11.7 (c 2.9, $CHCl_3$) (lit.[16] $[\alpha]_D^{21}$ +12.3 (c 1.7, $CHCl_3$)); δ_H (400 MHz, $CDCl_3$) 1.06 (9H, s, *t*-Bu), 1.30 (3H, t, J 7.2 Hz, OCH_2CH_3), 3.38 (3H, s, OMe), 3.69 (1H, dd, J 11.1, 5.0 Hz, 5-*H*H), 3.77 (1H, dd, J 11.1, 6.2 Hz, 5-H*H*), 4.22 (2H, q, J 7.2 Hz, OCH_2CH_3), 4.35–4.40 (1H, m, 4-H), 4.67 (1H, d, J 7.1 Hz, O*CH*HO), 4.72 (1H, d, J 7.1 Hz, OCH*H*O), 6.17 (1H, dd, J 16.3, 2.0 Hz, 2-H), 6.90 (1H, dd, J 16.3, 6.4 Hz, 3-H), 7.34–7.48 (6H, m, Ar–H), 7.56–7.72 (4H, m, Ar–H); δ_C (100 MHz, $CDCl_3$) 14.3 (CH_3), 19.2 (C), 26.8 (CH_3), 55.6 (CH_3), 60.5 (CH_2), 66.1 (CH_2), 76.0 (CH), 95.2 (CH_2), 122.8 (CH), 127.8 (CH), 129.8

(CH), 133.1 (C), 135.6 (CH), 145.1 (CH), 166.1 (C); *m*/*z* (CI) 443 (MH^+, 2%) 381 (100), 321 (7), 257 (16), 243 (15), 143 (10).

4.1.10. *(2E,4S)-5-(tert-Butyldiphenylsilyloxy)-4-(methoxymethoxy)pent-2-en-1-ol* **12**

Ethyl (2*E*,4*S*)-5-(*tert*-butyldiphenylsilyloxy)-4-(methoxymethoxy)pent-2-enoate **11** (2.8 g, 6 mmol) was dissolved in diethyl ether (50 mL) and cooled to −78 °C. DIBAL-H (1 M in hexanes) (14.0 mL, 14 mmol) was then added dropwise to the solution. The reaction mixture was stirred at −78 °C for 1 h and then warmed to room temperature overnight. The solution was then cooled to 0 °C and a saturated ammonium chloride solution (7 mL) was added. The reaction mixture was stirred for 1 h and then filtered under vacuum through Celite® to remove a white precipitate, which was then washed with diethyl ether (400 mL). The resulting filtrate was dried ($MgSO_4$) and concentrated to give a yellow oil. Purification by flash column chromatography (eluting with 50% diethyl ether/petroleum ether) yielded (2*E*,4*S*)-5-(*tert*-butyldiphenylsilyloxy)-4-(methoxymethoxy)pent-2-en-1-ol **12** as yellow oil (2.19 g, 86%). ν_{max}/cm^{-1} (neat) 3422 (OH), 2931 (CH), 1589 (C=C), 1472, 1428, 1112, 704; $[\alpha]_D^{28}$ +31.2 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.05 (9H, s, *t*-Bu), 1.29 (1H, br s, 1-OH), 3.37 (3H, s, OMe), 3.63 (1H, dd, *J* 11.1, 6.0 Hz, 5-*H*H), 3.74 (1H, dd, *J* 11.1, 7.6 Hz, 5-H*H*), 4.12 (2H, br d, *J* 5.0 Hz, 1-H_2), 4.18–4.24 (1H, m, 4-H), 4.64 (1H, d, *J* 7.1 Hz, OC*H*HO), 4.70 (1H, d, *J* 7.1 Hz, OCH*H*O), 5.58 (1H, ddt, *J* 16.3, 8.0, 2.1 Hz, 3-H), 6.80 (1H, dtd, *J* 16.3, 5.0, 1.0 Hz, 2-H), 7.36–7.46 (6H, m, Ar–H), 7.66–7.72 (4H, m, Ar–H); δ_C (100 MHz, $CDCl_3$) 19.3 (C), 26.8 (CH_3), 55.4 (CH_3), 63.0 (CH_2), 66.8 (CH_2), 76.8 (CH), 94.4 (CH_2), 127.7 (CH), 128.5 (CH), 129.7 (CH), 132.9 (CH), 133.5 (C), 135.7 (CH); *m*/*z* (CI) 401 (MH^+, 3%) 339 (100), 261 (24), 209 (25), 167 (21), 143 (19), 117 (29).

4.1.11. *Rearrangement of* **13** *using* $PtCl_2$

(2*E*,4*S*)-5-(*tert*-Butyldiphenylsilyloxy)-4-(methoxymethoxy)-pent-2-en-1-ol **12** (0.3 g, 0.75 mmol) was dissolved in dichloromethane (20 mL) and cooled to 0 °C. Diazabicyclo[5.4.0]undec-7-ene (0.13 mL, 0.9 mmol) was then added to the solution followed by the addition of trichloroacetonitrile (0.1 mL, 1.1 mmol). The reaction was warmed to room temperature and stirred for 2 h. The reaction mixture was then filtered through a short pad of silica gel and washed with diethyl ether (200 mL). The resulting filtrate was then concentrated to give allylic trichloroacetimidate **13** as a brown oil (0.41 g) that was used without further purification. δ_H (400 MHz, $CDCl_3$) 1.04 (9H, s *t*-Bu), 3.36 (3H, s, OMe), 3.64 (1H, dd, *J* 10.5, 5.1 Hz, 5-*H*H), 3.75 (1H, dd, *J* 10.5, 6.4 Hz, 5-H*H*), 4.23 (1H, q, *J* 6.4 Hz, 4-H), 4.64 (1H, d, *J* 6.7 Hz, OC*H*HO), 4.70 (1H, d, *J* 6.7 Hz, OCH*H*O), 4.78 (2H, d, *J* 5.5 Hz, 1-H_2), 5.79 (1H, dd, *J* 15.7, 6.4 Hz, 3-H), 5.93 (1H, dt, *J* 15.7, 5.5 Hz, 2-H), 7.35–7.45 (6H, m, Ar–H), 7.66–7.71 (4H, m, Ar–H), 8.32 (1H, br s, NH). Allylic trichloroacetimidate **13** (0.41 g, 0.75 mmol) was dissolved in toluene (10 mL) under a nitrogen atmosphere. Platinum(II) chloride (0.02 g, 0.08 mmol) was then added to the solution and the reaction mixture was stirred at room temperature overnight. The reaction mixture was then filtered through a short pad of Celite®, washed with diethyl ether (100 mL) and concentrated under vacuum. Purification by flash column chromatography (elution with 5% diethyl ether/petroleum ether) gave (3*R*,4*S*)-5-(*tert*-butyldiphenylsilyloxy)-4-methoxymethoxy-3-(trichloromethylcarbonylamino)pent-1-ene **14** as a colourless oil. Further elution with 5% diethyl ether/petroleum ether gave (3*S*,4*S*)-5-(*tert*-butyldiphenylsilyloxy)-4-methoxymethoxy-3-(trichloromethylcarbonylamino)pent-1-ene **15** as a colourless oil (0.105 g, 25% combined yield, 1:4 ratio). *Data for* ***14***: ν_{max}/cm^{-1} (neat) 3393 (NH), 2931 (CH), 1717 (CO), 1645 (C=C), 1428, 1113, 1032, 822; $[\alpha]_D^{25}$ +5.7 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.09 (9H, s, *t*-Bu), 3.30 (3H, s, OMe), 3.65 (1H, dd, *J* 11.1, 8.0 Hz, 5-*H*H), 3.73 (1H, dd, *J* 11.1, 7.3 Hz, 5-H*H*), 3.88–3.92 (1H, m, 4-H), 4.62 (1H, d, *J* 7.1 Hz, OC*H*HO), 4.67 (1H, d, *J* 7.1 Hz, OCH*H*O), 4.81–4.84 (1H, m, 3-H), 5.31–5.38 (2H, m, 1-H_2), 5.93 (1H, ddd, *J* 17.2, 10.5, 5.0 Hz, 2-H), 7.17 (1H, br d, *J* 8.4 Hz, NH), 7.38–7.59 (6H, m, Ar–H), 7.64–7.62 (4H, m, Ar–H); δ_C (100 MHz, $CDCl_3$) 19.2 (C), 26.8 (CH_3), 53.5 (CH_3), 55.9 (CH), 63.0 (CH_2), 78.0 (CH), 93.1 (C), 96.6 (CH_2), 116.8 (CH_2), 127.9 (CH), 129.9 (CH), 132.7 (C), 134.6 (CH), 135.6 (CH), 161.5 (C); found (CI): 546.1225, $C_{25}H_{33}NO_4{}^{35}Cl_2{}^{37}ClSi$ requires MH^+ 546.1220; *Data for* ***15***: ν_{max}/cm^{-1} (neat) 3393 (NH), 2931 (CH), 1717 (CO), 1645 (C=C), 1428, 1113, 1032, 822; $[\alpha]_D^{25}$ −28.1 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.10 (9H, s, *t*-Bu), 3.40 (3H, s, OMe), 3.65–3.81 (3H, m, 5-H_2 and 4-H), 4.64 (1H, d, *J* 6.7 Hz, OC*H*HO), 4.69 (1H, d, *J* 6.7 Hz, OCH*H*O), 4.71–4.76 (1H, m, 3-H), 5.30 (1H, dt, *J* 10.4, 1.2 Hz, 1-*H*H), 5.36 (1H, dt, *J* 17.1, 1.2 Hz, 1-H*H*), 5.79 (1H, ddd, *J* 17.1, 10.4, 6.6 Hz, 2-H), 7.40–7.49 (6H, m, Ar–H), 7.68–7.73 (4H, m, Ar–H), 8.04 (1H, br d, *J* 8.0 Hz, NH); δ_C (100 MHz, $CDCl_3$) 19.2 (C), 26.9 (CH_3), 54.4 (CH_3), 55.9 (CH), 63.8 (CH_2), 81.7 (CH), 92.9 (C), 97.7 (CH_2), 118.8 (CH_2), 127.8 (CH), 129.9 (CH), 131.6 (CH), 132.9 (C), 135.6 (CH), 161.4 (C); found (CI): 546.1225, $C_{25}H_{33}NO_4{}^{35}Cl_2{}^{37}ClSi$ requires MH^+ 546.1220.

4.1.12. *Rearrangement of* **13** *using* $HAuCl_3 \cdot 3H_2O$

The reaction was carried out as described above using (2*E*,4*S*)-5-(*tert*-butyldiphenylsilyloxy)-4-(methoxymethoxy)pent-2-en-1-ol **12** (0.05 g, 0.13 mmol) and hydrogen tetrachloroaurate(III) hydrate (10 mol %). Flash column chromatography (elution with 5% diethyl ether/petroleum ether) gave **14**, followed by **15** as colourless oil (0.03 g, 49% combined yield, 1:2 ratio). Spectroscopic data as described above.

4.1.13. *Rearrangement of* **13** *using AuCl*

The reaction was carried out as described above using (2*E*,4*S*)-5-(*tert*-butyldiphenylsilyloxy)-4-(methoxymethoxy)pent-2-en-1-ol **12** (0.1 g, 0.5 mmol) and gold(I) chloride (10 mol %). Flash column chromatography (elution with 5% diethyl ether/petroleum ether) gave **14** followed by **15** as colourless oil (0.06 g, 40% combined yield, 1:3 ratio). Spectroscopic data as described above.

4.1.14. *Rearrangement of* **13** *using* $PdCl_2(MeCN)_2$

The reaction was carried out as described above using (2*E*,4*S*)-5-(*tert*-butyldiphenylsilyloxy)-4-(methoxymethoxy)pent-2-en-1-ol **12** (0.14 g, 0.25 mmol) and bis(acetonitrile)palladium(II) chloride (10 mol %). Flash column chromatography (elution with 5% diethyl ether/petroleum ether) gave **14** followed by **15** as colourless oil (0.13 g, 68% combined yield, 1:4 ratio of diastereomers). Spectroscopic data as described above.

4.1.15. *Rearrangement of* **13** *using (R)-COP-Cl*

The reaction was carried out as described above using (2*E*,4*S*)-5-(*tert*-butyldiphenylsilyloxy)-4-(methoxymethoxy)pent-2-en-1-ol **12** (0.14 g, 0.25 mmol), (*R*)-COP-Cl (10 mol %) and dichloromethane (10 mL) as the solvent. Flash column chromatography (elution with 5% diethyl ether/petroleum ether) gave **14** followed by **15** as colourless oil (0.13 g, 68% combined yield, 1:16 ratio of diastereomers). Spectroscopic data as described above.

4.1.16. *(2R,3S)-4-(tert-Butyldiphenylsilyloxy)-3-methoxymethoxy-2-(trichloromethylcarbonylamino)butanoic acid* ***16***

(3*S*,4*S*)-5-(*tert*-Butyldiphenylsilyloxy)-4-methoxymethoxy-3-(trichloromethylcarbonylamino)pent-1-ene **15** (0.2 g, 0.37 mmol) was dissolved in tetrachloromethane (7 mL) and acetonitrile (7 mL). Sodium periodate (0.32 g, 1.5 mmol) in water (11 mL) was then added to the solution. Ruthenium trichloride hydrate (4 mg, 0.03 mmol) was then added to the biphasic solution and the reaction mixture was then stirred vigorously at room temperature overnight. The reaction mixture was then extracted with dichloromethane (4×40 mL), dried ($MgSO_4$) and concentrated in vacuo to yield the

crude product. The compound was then dissolved in an aqueous solution of sodium hydrogen carbonate (10 mL), extracted with ethyl acetate (2×10 mL) and re-acidified by addition of 2 M hydrochloric acid (15 mL). The aqueous phase was extracted with ethyl acetate (5×10 mL), dried ($MgSO_4$) and concentrated in vacuo to give (2*R*,3*S*)-4-(*tert*-butyldiphenylsilyloxy)-3-methoxymethoxy-2-(trichloromethylcarbonylamino)butanoic acid **16** (0.15 g, 71%) as a colourless oil. ν_{max}/cm^{-1} (neat) 3334 (NH and OH), 2958 (CH), 1652 (CO), 1110, 1027, 820; $[\alpha]_D^{24}$ −12.5 (*c* 1.5, MeOH); δ_H (400 MHz, CD_3OD) 0.98 (9H, s, *t*-Bu), 3.24 (3H, s, OMe), 3.85 (1H, dd, *J* 10.8, 6.3 Hz, 4-*H*H), 3.92 (1H, dd, *J* 10.8, 4.6 Hz, 4-H*H*), 3.98–4.02 (1H, m, 3-H), 4.50 (1H, d, *J* 3.0 Hz, 2-H) 4.56 (1H, d, *J* 6.8 Hz, OC*H*HO), 4.58 (1H, d, *J* 6.8 Hz, OCH*H*O), 7.22–7.36 (6H, m, Ar–H), 7.58–7.63 (4H, m, Ar–H); δ_C (100 MHz, CD_3OD) 20.1 (C), 27.2 (CH_3), 56.4 (CH_3), 57.8 (CH), 65.8 (CH_2), 80.5 (CH), 93.8 (C), 98.2 (CH_2), 128.6 (CH), 130.9 (CH), 134.5 (C), 136.8 (CH), 163.0 (C), 173.3 (C); *m*/*z* (CI) 562 (MH^+, 3%), 472 (4), 376 (5), 325 (10), 274 (100), 196 (30).

4.1.17. (2R,3S)-2-Amino-3,4-dihydroxybutyric acid **1**[17]

(2*R*,3*S*)-4-(*tert*-Butyldiphenylsilyloxy)-3-methoxymethoxy-2-(trichloromethylcarbonylamino)butanoic acid **16** (0.12 g, 0.20 mmol) was dissolved in THF (10 mL). Tetrabutylammonium fluoride (1.0 M solution in THF) (0.73 mL, 0.73 mmol) was then added and the solution was stirred at room temperature overnight. The reaction mixture was then concentrated and the residue redissolved in ethyl acetate (15 mL). This was washed with water (15 mL), and then the organic layer was dried ($MgSO_4$) and concentrated to give a brown oil (0.1 g). This oil was then dissolved in 6 M hydrochloric acid solution (10 mL) and heated under reflux overnight. The reaction mixture was cooled to room temperature and then extracted with diethyl ether (10 mL). The aqueous phase was then concentrated in vacuo to give the crude product. Purification by ion exchange chromatography (elution with 0.5 M NH_4OH solution) yielded (2*R*,3*S*)-2-amino-3,4-dihydroxybutyric acid **1** as a white solid (11 mg, 44% over two steps). $[\alpha]_D^{24}$ +10.6 (*c* 0.5, H_2O) (lit.[17] $[\alpha]_D^{25}$ +11.4 (*c* 7.0, H_2O)); δ_H (400 MHz, D_2O) 3.58–3.69 (2H, m, 4-H_2), 3.85 (1H, d, *J* 4.0 Hz, 2-H), 3.98–4.04 (1H, m, 3-H); *m*/*z* (CI) 136 (MH^+, 5%), 130 (100), 114 (30), 69 (29).

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