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Synthesis and reactivity of 4-oxo-5-trimethylsilanyl derived α-amino acids

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ABSTRACT

A Lewis-acid promoted one-carbon homologation of an aspartic acid semialdehyde with trimethylsilyldiazomethane has led to the efficient synthesis of two silicon-containing α-amino acids. The use of trimethylaluminium or catalytic tin(II) chloride gave novel 4-oxo-5-trimethylsilanyl derived amino acids in yields of 71–88%. An investigation into the reactivity of these highly functional α-amino acids showed that selective cleavage of the C–Si bond could be achieved under mild basic conditions to give a protected derivative of the naturally occurring amino acid, 4-oxo-L-norvaline. Alternatively, Peterson olefination with aryl or alkyl aldehydes resulted in the formation of *E*-enone derived α-amino acids.

1. Introduction

α-Amino acids are the structural building blocks of life, serving as the key components of all proteins and enzymes.[1] They also play an important role in many enzymatic reactions and in signal induction pathways. This importance in combination with the rapid and continual advances in the biomedical sciences has required the development of novel approaches to optically active α-amino acids and in particular functional, non-proteinogenic analogues.[2] As well as being used to probe the mechanism of enzymes and study the bioactive conformations of peptides and proteins, these compounds often have significant pharmacological properties.

In this regard, unnatural silicon-containing α-amino acids and peptides have found many applications in structural biology and medicinal chemistry.[3] The inclusion of a silicon-containing group has been shown to improve lipophilicity, while silicon analogues of proteinogenic α-amino acids such as β-trimethylsilyl alanine (**1**)[4] and γ-(dimethylsila)proline (**2**)[5] have demonstrated increased resistance to proteolytic degradation and increased cellular uptake, respectively (Fig. 1). A number of silicon-containing bio-isosteres with enhanced stability have been utilised for the development of therapeutically active peptides.[3] For example, a disilanol analogue of phenylalanine has been used as a transition-state-like hydrated carbonyl for the generation of a highly potent angiotensin-converting enzyme inhibitor **3**.[6]

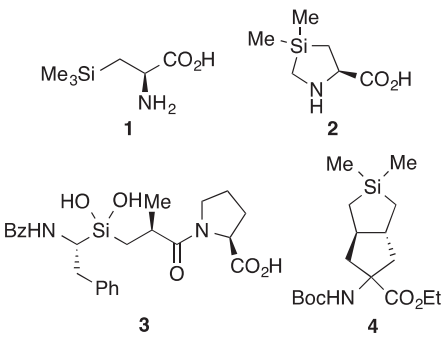

Fig. 1. Silicon-containing α-amino acids and peptides.

Despite their enhanced stability and advantageous pharmacological properties, synthetic routes towards silicon-containing amino acids are still relatively limited in number.[3,7] Noteworthy approaches include the use of a reverse aza-Brook rearrangement of allyl and furyl *N*-trialkylsilyl amines for the synthesis of α-trialkylsilyl α-amino acids.[8] More recently, Cavelier and co-workers prepared γ-silylated α-amino acids by a platinum-catalysed hydrosilylation of unsaturated precursors,[7b] while Ramesh and Reddy used a zinc mediated allylation of a chlorosilane as the key

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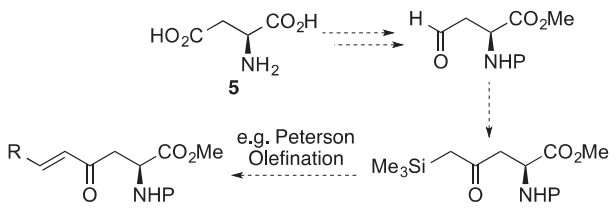
step for the preparation of unusual 5,5-*trans* fused α-amino acid derivative **4** (Fig. 1).[7h]

During a recent study into the synthesis of α-amino acids bearing ketone side-chains, we unexpectedly formed stable 4-oxo-5-trimethylsilanyl compounds derived from L-aspartic acid. Following further investigation of this serendipitous result, we now report the highly efficient synthesis of these compounds by the one-carbon homologation of *N*-Boc-protected aspartic acid semialdehydes with trimethylsilyldiazomethane in the presence of a Lewis acid. We also describe a preliminary study of the reactivity of these compounds with a novel synthesis of a 4-oxo-L-norvaline derivative, and the preparation of *E*-enone derived α-amino acids via Peterson olefination.

2. Results and discussion

As outlined in Scheme 1, our proposed approach to 4-oxo-5-trimethylsilanyl derived α-amino acids involved the rapid and efficient protection of L-aspartic acid (**5**) using a protecting group strategy that would allow the selective reduction of the β-carbonyl moiety. The resulting aspartic acid semialdehyde would then be used to investigate the formation of the target oxotrialkylsilane by a one-carbon homologation reaction with trimethylsilyldiazomethane. Once this step had been optimised, it was proposed that these types of compounds could be used as building blocks for the preparation of more elaborate side-chains.

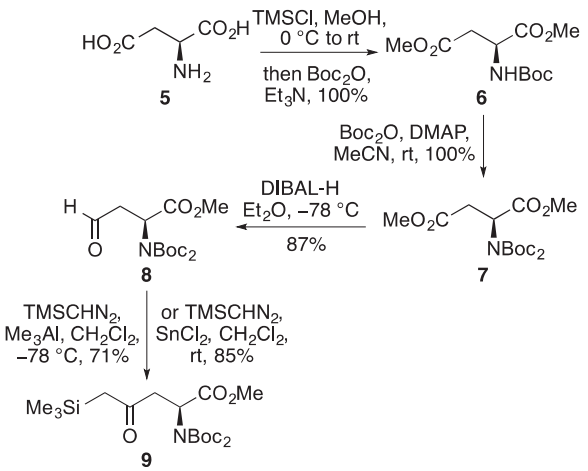


Scheme 1. Proposed approach to 4-oxo-5-trimethylsilanyl derived α-amino acids from L-aspartic acid (**5**).

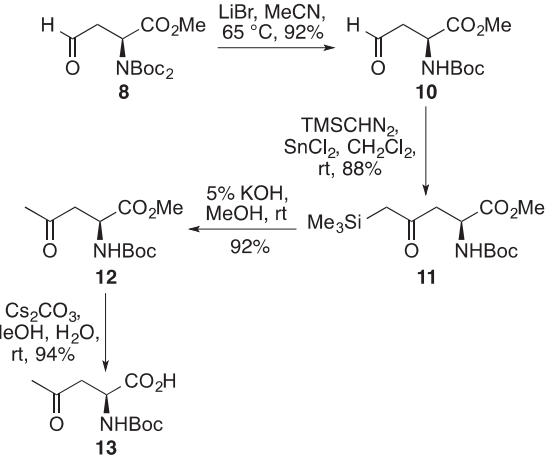
It was decided to use di-Boc aspartic acid semialdehyde **8**, the synthesis of which was first reported by Martín and co-workers[9a] and has been used by others for the preparation of a range of unnatural α-amino acids.[9] *N*,*N*′-Di-*tert*-butoxycarbonyl L-aspartic acid dimethyl ester (**7**) was initially prepared in two steps from L-aspartic acid (**5**) (Scheme 2). A one-pot esterification and mono-*N*-Boc protection was followed by further reaction with di-*tert*-butyl dicarbonate and a catalytic amount of DMAP, which gave **7** in quantitative yield. Using the steric bulk of the bis-protected amine, regioselective reduction of the β-methyl ester was then achieved using DIBAL-H. This allowed the isolation of aspartic acid semialdehyde **8** in 87% yield.

With semialdehyde **8** in hand, methods for conversion to the corresponding 4-oxo-5-trimethylsilanyl derivative **9** were next investigated. In 1987, Aoyama and Shioiri demonstrated that 2-oxotrialkylsilanes could be formed from the reaction of aldehydes with trimethylsilyldiazomethane in the presence of magnesium bromide.[10] More recently, Lee and co-workers reported a similar reaction using catalytic indium(III) chloride (2 mol %) that gave high yields of 2-trimethylsilyl ketones.[11] In these transformations, the Lewis acid-activated aldehyde is subjected to nucleophilic attack by trimethysilyldiazomethane. The resulting intermediate then undergoes a 1,2-hydride shift with simultaneous extrusion of nitrogen and formation of the 2-oxotrialkylsilane. In both of these studies, quenching the reaction with dilute acid or purification by silica gel flash chromatography was avoided to prevent protodesilylation and formation of the corresponding methyl ketones.[12] Using the Aoyama procedure with semialdehyde **8**, trimethylsilyldiazomethane and a stoichiometric amount of magnesium bromide returned mainly starting material. However, the use of a stronger Lewis acid such as trimethylaluminium[13] allowed clean conversion to 4-oxo-5-trimethylsilane **9** (Scheme 2). Surprisingly, **9** was found to be stable to protodesilylation. Work-up of this reaction with an acid wash (0.1 M HCl) and purification by silica gel flash chromatography gave 4-oxo-5-trimethylsilane **9** in 71% yield. A less pyrophoric Lewis acid was then investigated and the use of catalytic tin(II) chloride[14] (5 mol %) resulted in the isolation of 4-oxo-5-trimethylsilane **9** in an optimal yield of 85%.

While the synthesis of 4-oxo-5-trimethylsilane **9** was successfully achieved, we were concerned that subsequent reactions with this intermediate may be limited. Di-*N*-Boc-protected α-amino esters are known to racemise more easily under basic conditions due to the acidic nature of the α-hydrogen.[15] Furthermore, the steric bulk associated with the two *N*-Boc groups of α-amino acid derivatives can hinder reactions of the side-chain.[9g,16] Therefore, a mono-*N*-Boc-protected analogue of **9** was prepared (Scheme 3). Selective removal of one of the Boc protecting groups from aspartic acid semialdehyde **8** was achieved using lithium bromide under the conditions reported by Martín and co-workers.[17] This generated the mono-*N*-Boc-protected analogue **10** in 92% yield. Reaction of **10** with trimethylsilyldiazomethane and tin(II) chloride (5 mol %) gave 4-oxo-5-trimethylsilane **11** in an excellent 88% yield. Like di-*N*-Boc analogue **9**, 4-oxo-5-trimethylsilane **11** was isolated using an acidic work-up (0.1 M HCl) and purified by silica gel flash



Scheme 2. Four-step synthesis of 4-oxo-5-trimethylsilanyl derived α-amino acid **9**.



Scheme 3. Synthesis of 4-oxo-5-trimethylsilane **11** and conversion to 4-oxo-L-norvaline derivative **13**.

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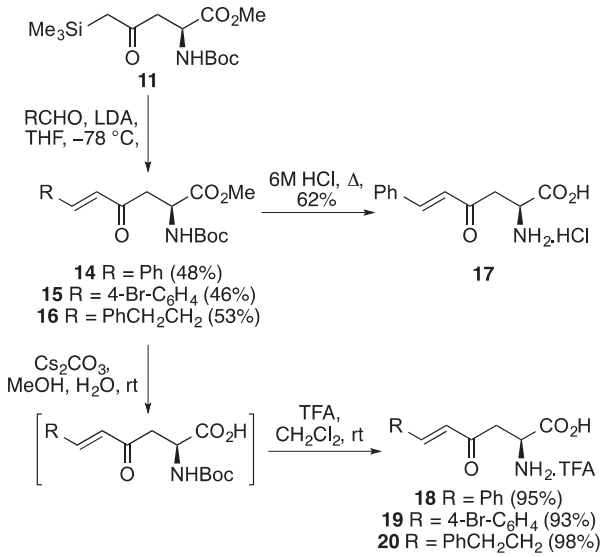
chromatography. The relative stability of the di-*N*-Boc-protected 4-oxo-5-trimethylsilane **9** was reasoned due to the substantial steric bulk associated with the two Boc protecting groups. However, the facile and high yielding synthesis of mono-*N*-Boc-protected 4-oxo-5-trimethylsilane **11** shows that unhindered oxotrialkylsilanes of this type are stable enough to be isolated.[18]

Having prepared 4-oxo-5-trimethylsilanyl derived amino acid **11**, we were interested in examining the reactivity of this compound for the synthesis of biologically and synthetically useful α-amino acids. The first target was 4-oxo-L-norvaline, a rare ketone-substituted α-amino acid produced as a metabolite from ornithine by *Clostridium sticklandii* and in bone marrow by α-amino-levulinic acid synthetase.[19] The biological importance of this α-amino acid has resulted in a number of syntheses,[13b,20] as well as an investigation into its use as an inhibitor of oligosaccharyltransferase.[20f] It was proposed that protodesilylation of 4-oxo-5-trimethylsilane **11** would result in a short synthesis of 4-oxo-L-norvaline derivatives (Scheme 3). While protodesilylation is normally performed under acidic conditions,[10] we wanted to maintain the *N*-Boc protecting group. Therefore, initial attempts at cleavage of the C–Si bond were conducted under basic conditions. Treatment of 4-oxo-5-trimethylsilane **11** with TBAF led to complete decomposition. However, selective removal of the trimethylsilyl group in the presence of the methyl ester was efficiently achieved with 5% potassium hydroxide, which gave 4-oxo-L-norvaline derivative **12** in 92% yield. The two-step, one-carbon homologation converting semialdehyde **10** to methyl ketone **12** represents a simple and highly efficient alternative to standard multi-step protocols.[10] Hydrolysis of **12** using caesium carbonate then gave *N*-Boc-protected 4-oxo-L-norvaline **13** in 94% yield. This is a form of 4-oxo-L-norvaline that is used for peptide synthesis[20f] and the approach described here allows a seven-step preparation in 61% overall yield.

A study has also been performed to evaluate the use of 4-oxo-5-trimethylsilane **11** as a substrate in the Peterson olefination for the synthesis of *E*-enone derived α-amino acids. α-Amino acids bearing an enone side-chain have many applications.[21] These include their use in 6-*endo*- or 6-*exo*-*trig* cyclisations for the stereoselective synthesis of highly substituted pipecolic acids.[22] Initial attempts at Peterson olefination of 4-oxo-5-trimethylsilane **11** with benzaldehyde using either lithium diisopropylamide (LDA) or lithium bis(trimethylsilyl)amide (LiHMDS) led to only substantial decomposition of **11**. After careful experimentation, it was found that the order of reagent addition was crucial for success. In situ formation of LDA and dropwise addition via cannula to a THF solution of 4-oxo-5-trimethylsilane **11** at −78 °C, followed by the addition of benzaldehyde gave *E*-enone **14** in 48% yield (Scheme 4). At this stage, the enantiopurity of enone **14** was determined to check that the integrity of the stereocentre had been retained during the stages of the synthetic route where di-*N*-Boc compounds has been generated and through the use of LDA. A comparison of (2*S*)-**14** and racemic-**14** (prepared from D/L-aspartic acid) using chiral HPLC showed the enantiomeric excess of (2*S*)-**14** was >99% ee, confirming that no racemisation had taken place during the synthetic route.[23] Following this result, the scope of the Peterson reaction was extended to two further analogues. Reaction of **11** with 4-bromobenzaldehyde and hydrocinnamaldehyde gave the corresponding enones **15** and **16** in comparable yields. NMR spectroscopy of the crude material from the Peterson reactions showed only the presence of the *E*-isomer, demonstrating a highly selective process.

Methods for the deprotection of enones **14**–**16** were then investigated. For example, a one-step procedure was demonstrated for removal of both the Boc protecting group and hydrolysis of the methyl ester of enone **14** using 6 M HCl under reflux conditions (Scheme 4). Following recrystallisation, amino acid **17** was isolated in 62% yield. However, a more efficient approach was possible using



Scheme 4. Synthesis of *E*-enone derived α-amino acids **18**–**20** via Peterson olefination of 4-oxo-5-trimethylsilane **11**.

a stepwise deprotection approach. Hydrolysis of the ester using caesium carbonate, followed by TFA-mediated removal of the Boc group under mild conditions gave after recrystallisation, enone derived α-amino acids **18**–**20** in 93–98% yield over the two steps. This approach also has the advantage of generating the *N*-Boc-protected α-amino acids after the first step, which could have direct application in peptide synthesis.

3. Conclusions

In summary, two novel 4-oxo-5-trimethylsilanyl derived α-amino acids have been prepared by the reaction of aspartic acid semialdehydes with trimethylsilyldiazomethane in the presence of Lewis acids. In particular, the use of catalytic tin(II) chloride allowed the synthesis of these compounds in excellent yields. Unlike similar 2-oxo-trimethylsilanes, these compounds were found to be relatively stable to protodesilylation and could be isolated using a dilute acid work-up and purified by silica gel flash column chromatography. Based on this relative stability, preliminary studies into the synthetic utility of these compounds have been conducted. Selective cleavage of the C–Si bond of 4-oxo-5-trimethylsilane **11** was achieved under mild basic conditions generating derivatives of the non-proteinogenic α-amino acid, 4-oxo-L-norvaline. Alternatively, Peterson olefination of **11** with LDA and various aldehydes led to the preparation of *E*-enones as the sole products in good yields. Work to investigate further synthetic and biological applications of the 4-oxo-5-trimethylsilanyl derived α-amino acids generated from this study, including their use as structural analogues in therapeutic peptides, 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. Brine refers to a saturated solution of sodium chloride. 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 (ppm) relative to TMS (δ_H 0.00 and δ_C 0.0) or residual chloroform (δ_H 7.28 and δ_C 77.2) as standard. Proton and carbon assignments are based on two-dimensional COSY and DEPT experiments, respectively. Mass spectra were obtained using a JEOL JMS-700 spectrometer. Infrared spectra were obtained neat using a Shimadzu IRPrestige-21 spectrometer. Melting points were determined on a Reichert platform melting point apparatus. Optical rotations were determined as solutions irradiating with the sodium D line (λ=589 nm) using an Autopol V polarimeter. $[\alpha]_D$ values are given in units 10^{-1} deg cm^2 g^{-1}.

4.2. Dimethyl (2*S*)-2-(*tert*-butoxycarbonylamino)butane-1,4-dioate (6)[9a]

Chlorotrimethylsilane (21.2 mL, 165.4 mmol) was added slowly to a stirred suspension of L-aspartic acid (**5**) (5.00 g, 37.6 mmol) in methanol (100 mL) at 0 °C. The reaction mixture was allowed to stir for 1 h at 0 °C and then at room temperature for 24 h. Triethylamine (34.0 mL, 244.4 mmol) and di-*tert*-butyl dicarbonate (9.02 g, 41.4 mmol) were added slowly and the mixture stirred for 2 h. The reaction mixture was concentrated in vacuo and the resulting residue dissolved in diethyl ether (200 mL) and filtered to remove the white precipitate. The filtrate was concentrated in vacuo and purified using flash column chromatography (35% ethyl acetate in petroleum ether) to yield dimethyl (2*S*)-2-(*tert*-butoxycarbonylamino)butane-1,4-dioate (**6**) as a white solid (9.81 g, 100%). Mp 58–60 °C; ν_{max} (NaCl) 3406 (NH), 2927 (CH), 2360, 1704 (C=O), 1458, 1159, 1045 cm^{-1}; $[\alpha]_D^{25}$ +35.8 (*c* 1.0, $CHCl_3$), lit.[9a] $[\alpha]_D^{25}$ +30.8 (*c* 2.1, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.47 (9H, s, ^{t}Bu), 2.85 (1H, dd, *J* 16.8, 4.2 Hz, 3-*H*H), 3.03 (1H, dd, *J* 16.8, 4.2 Hz, 3-H*H*), 3.72 (3H, s, OMe), 3.78 (3H, s, OMe), 4.58–4.61 (1H, m, 2-H), 5.50 (1H, br d, *J* 8.4 Hz, NH); δ_C (101 MHz, $CDCl_3$) 28.3 (3×CH_3), 36.7 (CH_2), 49.9 (CH), 52.1 (CH_3), 52.8 (CH_3), 80.2 (C), 155.4 (C), 171.5 (C), 171.6 (C); *m*/*z* (CI) 262 (MH^+, 15%), 206 (100), 162 (36), 85 (13); HRMS (CI): MH^+, found 262.1293. $C_{11}H_{20}NO_6$ requires 262.1291.

4.3. Dimethyl (2*S*)-2-(di-*tert*-butoxycarbonylamino)butane-1,4-dioate (7)[9a]

Dimethyl (2*S*)-2-(*tert*-butoxycarbonylamino)butane-1,4-dioate (0.90 g, 3.50 mmol) (**6**) was dissolved in acetonitrile (50 mL). 4-Dimethylaminopyridine (0.08 g, 0.70 mmol) and di-*tert*-butyl dicarbonate (0.80 g, 3.80 mmol) were added and the reaction mixture was allowed to stir at room temperature for 3 h. A further quantity of di-*tert*-butyl dicarbonate (0.40 g, 1.90 mmol) was added and the mixture was allowed to stir at room temperature for 24 h. The solvent was removed in vacuo and the crude product was purified using flash column chromatography (20% ethyl acetate in petroleum ether) to yield dimethyl (2*S*)-2-(di-*tert*-butoxycarbonylamino)butane-1,4-dioate (**7**) as a white solid (1.25 g, 100%). Mp 55–57 °C; ν_{max} (NaCl) 2857 (CH), 1747 (C=O), 1458, 1375, 1145 cm^{-1}; $[\alpha]_D^{25}$ −61.5 (*c* 2.0, $CHCl_3$), lit.[9a] $[\alpha]_D^{25}$ −61.0 (*c* 2.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.53 (18H, s, 2×^{t}Bu), 2.77 (1H, dd, *J* 16.4, 6.4 Hz, 3-*H*H), 3.29 (1H, dd, *J* 16.4, 7.2 Hz, 3-H*H*), 3.73 (3H, s, OMe), 3.76 (3H, s, OMe), 5.48 (1H, dd, *J* 7.2, 6.4 Hz, 2-H); δ_C (101 MHz, $CDCl_3$) 28.0 (6×CH_3), 35.7 (CH_2), 52.0 (CH_3), 52.6 (CH_3), 54.9 (CH), 83.6 (2×C), 151.6 (2×C), 170.3 (C), 171.1 (C); *m*/*z* (CI) 362 (MH^+, 6%), 306 (38), 250 (33), 206 (100), 162 (50); HRMS (CI): MH^+, found 362.1819. $C_{16}H_{28}NO_8$ requires 362.1815.

4.4. Methyl (2*S*)-2-(di-*tert*-butoxycarbonylamino)-4-oxobutanoate (8)[9a]

Dimethyl (2*S*)-2-(di-*tert*-butoxycarbonylamino)butane-1,4-dioate (**7**) (6.90 g, 19.1 mmol) was dissolved in diethyl ether (150 mL) and cooled to −78 °C. DIBAL-H (26.8 mL, 26.8 mmol) was added dropwise and the solution was allowed to stir at −78 °C for 24 h. A saturated solution of ammonium chloride was added (40 mL) and the reaction mixture was allowed to warm to room temperature. It was filtered through a pad of Celite® with diethyl ether (300 mL) and concentrated in vacuo. Following purification by column chromatography (10% ethyl acetate in petroleum ether), methyl (2*S*)-2-(di-*tert*-butoxycarbonylamino)-4-oxobutanoate (**8**) was obtained as a colourless oil (5.50 g, 87%). ν_{max} (NaCl) 3132, 2796 (CH), 1782 (C=O), 1678, 1199, 1072 cm^{-1}; $[\alpha]_D^{26}$ −49.2 (*c* 3.4, $CHCl_3$), lit.[9a] $[\alpha]_D^{25}$ −54.9 (*c* 2.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.53 (18H, s, 2×^{t}Bu), 2.86 (1H, ddd, *J* 18.0, 6.0, 1.2 Hz, 3-*H*H), 3.45 (1H, ddd, *J* 18.0, 6.8, 1.2 Hz, 3-H*H*), 3.76 (3H, s, OMe), 5.57 (1H, dd, *J* 6.8, 6.0 Hz, 2-H), 9.82 (1H, br t, *J* 1.2 Hz, 4-H); δ_C (101 MHz, $CDCl_3$) 27.9 (6×CH_3), 45.0 (CH_2), 52.6 (CH_3), 52.9 (CH), 83.7 (2×C), 151.7 (2×C), 170.2 (C), 198.4 (C); *m*/*z* (CI) 332 (MH^+, 8%), 276 (60), 236 (51), 220 (100), 192 (98), 176 (86), 132 (26); HRMS (CI): MH^+, found 332.1708. $C_{15}H_{26}NO_7$ requires 332.1709.

4.5. Methyl (2S)-2-(di-*tert*-butoxycarbonylamino)-4-oxo-5-(trimethylsilanyl)pentanoate (9)

Methyl (2*S*)-2-(di-*tert*-butoxycarbonylamino)-4-oxobutanoate (**8**) (0.10 g, 0.30 mmol) was added to a solution of trimethylaluminium (0.20 mL, 0.40 mmol) in dichloromethane (10 mL) at −78 °C. Trimethylsilyldiazomethane (0.20 mL, 0.30 mmol) was added and the reaction mixture stirred at −78 °C for 1 h and then at −40 °C for 1 h. The solution was then poured into 0.1 M hydrochloric acid (10 mL) and extracted using dichloromethane (3×15 mL). The organic layers were combined, dried ($MgSO_4$) and concentrated in vacuo. Purification by flash chromatography (20% ethyl acetate in petroleum ether) gave methyl (2*S*)-2-(di-*tert*-butoxycarbonylamino)-4-oxo-5-(trimethylsilanyl)pentanoate (**9**) as a pale yellow oil (0.09 g, 71%). ν_{max} (NaCl) 2980 (CH), 1795 (C=O), 1747 (C=O), 1144, 853 cm^{-1}; $[\alpha]_D^{25}$ −72.5 (*c* 0.4, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.01 (9H, s, $SiMe_3$), 1.56 (18H, s, 2×^{t}Bu), 2.08 (1H, d, *J* 10.4 Hz, 5-*H*H), 2.13 (1H, d, *J* 10.4 Hz, 5-H*H*), 2.62 (1H, dd, *J* 18.0, 5.6 Hz, 3-*H*H), 3.22 (1H, dd, *J* 18.0, 6.8 Hz, 3-H*H*), 3.56 (3H, s, OMe), 5.35–5.40 (1H, m, 2-H); δ_C (101 MHz, $CDCl_3$) 0.0 (3×CH_3), 29.1 (6×CH_3), 39.3 (CH_2), 46.7 (CH_2), 53.5 (CH), 55.2 (CH_3), 84.4 (2×C), 152.9 (2×C), 172.0 (C), 206.2 (C); *m*/*z* (CI) 418 (MH^+, 16%), 346 (53), 318 (78), 262 (95), 234 (99), 218 (25), 190 (100), 146 (89); HRMS (CI): MH^+, found 418.2262. $C_{19}H_{36}NO_7Si$ requires 418.2261.

4.6. Methyl (2S)-2-(di-*tert*-butoxycarbonylamino)-4-oxo-5-(trimethylsilanyl)pentanoate (9)

Methyl (2*S*)-2-(di-*tert*-butoxycarbonylamino)-4-oxobutanoate (**8**) (0.10 g, 0.30 mmol) was dissolved in dichloromethane (10 mL). Tin(II) chloride (0.003 g, 0.015 mmol) and trimethylsilyldiazomethane (0.15 mL, 0.30 mmol) were added and the solution was allowed to stir at room temperature for 0.5 h. The reaction was quenched with 0.1 M hydrochloric acid (10 mL) and extracted with dichloromethane (20 mL). The organic layers were combined, washed with brine (20 mL), dried ($MgSO_4$) and concentrated in vacuo. Purification by flash chromatography (20% ethyl acetate in petroleum ether) gave methyl (2*S*)-2-(di-*tert*-butoxycarbonyl amino)-4-oxo-5-(trimethylsilanyl)pentanoate (**9**) as a pale yellow oil (0.09 g, 85%). Spectroscopic data as reported above.

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4.7. Methyl (2*S*)-2-(*tert*-butoxycarbonylamino)-4-oxobutanoate (10)[17]

Lithium bromide (2.33 g, 26.8 mmol) was added to a stirring solution of methyl (2*S*)-2-(di-*tert*-butoxycarbonylamino)-4-oxobutanoate (**8**) (2.90 g, 8.75 mmol) in acetonitrile (100 mL). The mixture was then heated at 65 °C for 14 h before being concentrated under reduced pressure. Purification by flash chromatography (30% ethyl acetate in hexane) gave methyl (2*S*)-2-(*tert*-butoxycarbonylamino)-4-oxobutanoate (**10**) as a colourless oil (1.86 g, 92%). $[\alpha]_D$ +20.4 (*c* 1.0, $CHCl_3$), lit.[17] $[\alpha]_D$ +16.4 (*c* 5.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.38 (9H, s, ^tBu), 2.95 (1H, dd, *J* 18.4, 4.6 Hz, 3-*H*H), 3.05 (1H, dd, *J* 18.4, 5.0 Hz, 3-H*H*), 3.69 (3H, s, OMe), 4.51–4.56 (1H, m, 2-H), 5.33 (1H, br d, *J* 7.6 Hz, NH), 9.67 (1H, br s, 4-H); δ_C (101 MHz, $CDCl_3$) 27.3 (3×CH_3), 45.0 (CH_2), 47.5 (CH), 51.8 (CH_3), 79.3 (C), 154.4 (C), 170.5 (C), 198.4 (C); *m*/*z* (CI) 232 (MH^+, 45%), 176 (100), 132 (79); HRMS (CI): MH^+, found 232.1181. $C_{10}H_{18}NO_5$ requires 232.1185.

4.8. Methyl (2*S*)-2-(*tert*-butoxycarbonylamino)-4-oxo-5-(trimethylsilanyl)pentanoate (11)

Tin(II) chloride (0.004 g, 0.021 mmol) was dried in an oven at 110 °C overnight and then under vacuum at 100 °C for 3 h in a round bottomed flask equipped with a stirrer bar. After the flask was cooled to room temperature and flushed with argon, a 2.0 M solution of trimethylsilyldiazomethane in diethyl ether (0.22 mL, 0.43 mmol) was added. A solution of methyl (2*S*)-2-(*tert*-butoxycarbonylamino)-4-oxobutanoate (**10**) (0.10 g, 0.43 mmol) in dichloromethane (4 mL) was then added dropwise with stirring. The mixture was stirred at room temperature for 1 h before water (5 mL) was added. The reaction was quenched with 0.1 M hydrochloric acid (3 mL) and extracted with diethyl ether (3×10 mL). The organic layers were combined, dried ($MgSO_4$) and concentrated in vacuo. Purification by flash chromatography (30% ethyl acetate in petroleum ether) gave methyl (2*S*)-2-(*tert*-butoxycarbonylamino)-4-oxo-5-(trimethylsilanyl)pentanoate (**11**) as a pale yellow oil (0.12 g, 88%). ν_{max} (NaCl) 3370 (NH), 2955 (CH), 1716 (C=O), 1499, 1253, 1168, 854 cm^{-1}; $[\alpha]_D^{26}$ +31.6 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.00 (9H, s, $SiMe_3$), 1.31 (9H, s, ^tBu), 2.08 (2H, s, 5-H_2), 2.79 (1H, dd, *J* 18.4, 4.0 Hz, 3-*H*H), 3.02 (1H, dd, *J* 18.4, 4.0 Hz, 3-H*H*), 3.60 (3H, s, OMe), 4.28–4.31 (1H, m, 2-H), 5.43 (1H, d, *J* 8.4 Hz, NH); δ_C (101 MHz, $CDCl_3$) 0.0 (3×CH_3), 29.5 (3×CH_3), 39.2 (CH_2), 47.2 (CH_2), 50.7 (CH), 53.7 (CH_3), 81.0 (C), 156.7 (C), 173.2 (C), 208.4 (C); *m*/*z* (CI) 318 (MH^+, 12%), 279 (31), 262 (100), 218 (46), 207 (71), 146 (21); HRMS (CI): MH^+, found 318.1740. $C_{14}H_{28}NO_5Si$ requires 318.1737.

4.9. Methyl (2*S*)-2-(*tert*-butoxycarbonylamino)-4-oxopentanoate (12)[24]

Methyl (2*S*)-2-(*tert*-butoxycarbonylamino)-4-oxo-5-(trimethylsilanyl)pentanoate (**11**) (0.10 g, 0.30 mmol) was dissolved in a 5% solution of potassium hydroxide in methanol (10 mL). This mixture was allowed to stir at room temperature for 1 h. The solvent was then removed under vacuum. The residue was dissolved in ethyl acetate (20 mL), dried ($MgSO_4$) and concentrated in vacuo. Purification by flash chromatography (50% ethyl acetate in petroleum ether) gave methyl (2*S*)-2-(*tert*-butoxycarbonylamino)-4-oxopentanoate (**12**) as a pale yellow oil (0.067 g, 92%). $[\alpha]_D^{25}$ +30.8 (*c* 2.1, $CHCl_3$), lit.[24] $[\alpha]_D^{22}$ +32.7 (*c* 1.0, $CHCl_3$); ν_{max} (neat) 3420 (NH), 3082 (CH), 1774 (C=O), 1612, 1466, 1111, 945 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.47 (9H, s, ^tBu), 2.20 (3H, s, 5-H_3), 2.98 (1H, dd, *J* 18.4, 4.2 Hz, 3-*H*H), 3.22 (1H, dd, *J* 18.4, 4.4 Hz, 3-H*H*), 3.76 (3H, s, OMe), 4.49–4.54 (1H, m, 2-H), 5.53 (1H, br d, *J* 8.4 Hz, NH); δ_C (101 MHz, $CDCl_3$) 28.3 (CH_3), 29.9 (3×CH_3), 45.4 (CH_2), 49.4 (CH), 52.7 (CH_3), 80.1 (C), 155.6 (C), 171.9 (C), 206.7 (C); *m*/*z* (FAB) 246 (MH^+, 45%), 190 (100), 147 (67), 89 (23); HRMS (FAB): MH^+, found 246.1343. $C_{11}H_{20}NO_5$ requires 246.1341.

4.10. (2*S*)-2-(*tert*-Butoxycarbonylamino)-4-oxopentanoic acid (13)[20f]

Methyl (2*S*)-2-(*tert*-butoxycarbonylamino)-4-oxopentanoate (**12**) (0.20 g, 0.70 mmol) was dissolved in a 1:1 mixture of methanol and water (20 mL). Caesium carbonate (0.30 g, 0.90 mmol) was added and the reaction mixture stirred at room temperature for 24 h. The mixture was acidified with 1 M hydrochloric acid (10 mL) and extracted with dichloromethane (3×10 mL). The organic layers were combined, dried ($MgSO_4$) and concentrated in vacuo to give (2*S*)-2-(*tert*-butoxycarbonylamino)-4-oxopentanoic acid (**13**) as a viscous colourless oil (0.15 g, 94%). Spectroscopic data were consistent with the literature.[20f] ν_{max} (neat) 3357 (NH), 3030 (CH), 1743 (C=O), 1688, 1456, 1138 cm^{-1}; $[\alpha]_D^{27}$ +26.1 (*c* 0.3, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.38 (9H, s, ^tBu), 2.13 (3H, s, 5-H_3), 2.88 (1H, dd, *J* 18.2, 4.8 Hz, 3-*H*H), 3.14 (1H, dd, *J* 18.2, 3.6 Hz, 3-H*H*), 4.46 (1H, ddd, *J* 8.4, 4.8, 3.6 Hz, 2-H), 5.48 (1H, br d, *J* 8.4 Hz, NH); δ_C (101 MHz, $CDCl_3$) 28.3 (3×CH_3), 30.0 (CH_3), 45.1 (CH_2), 49.3 (CH), 80.5 (C), 155.8 (C), 175.1 (C), 207.3 (C); *m*/*z* (CI) 232 (MH^+, 18%), 176 (100), 158 (33), 132 (95), 130 (36), 73 (40); HRMS (CI): MH^+, found 232.1189. $C_{10}H_{18}NO_5$ requires 232.1185.

4.11. Methyl (2*S*,5*E*)-2-(*tert*-butoxycarbonylamino)-4-oxo-6-phenylhex-5-enoate (14)[21f]

To a solution of diisopropylamine (0.12 mL, 0.84 mmol) in tetrahydrofuran (4 mL) at −78 °C was added dropwise, a solution of 2.5 M *n*-butyllithium in hexane (0.33 mL, 0.84 mmol). The mixture was stirred for 0.15 h before being added by cannula to a solution of methyl (2*S*)-2-(*tert*-butoxycarbonylamino)-4-oxo-5-(trimethylsilanyl)pentanoate (**11**) (0.12 g, 0.38 mmol) in tetrahydrofuran (5 mL). After 1 h, benzaldehyde (0.04 mL, 0.38 mmol) in tetrahydrofuran (3 mL) was added and the reaction mixture stirred for 5 h at −78 °C. The reaction was quenched by addition of a saturated solution of ammonium chloride (2.0 mL) and the mixture was warmed to room temperature. The solution was extracted with ethyl acetate (40 mL), washed with brine (20 mL), dried ($MgSO_4$) and concentrated in vacuo. Purification by flash chromatography (10% ethyl acetate in petroleum ether) gave methyl (2*S*,5*E*)-2-(*tert*-butoxycarbonyl amino)-4-oxo-6-phenylhex-5-enoate (**14**) a colourless oil (0.061 g, 48%). ν_{max} (NaCl) 3368 (NH), 2979 (CH), 1747 (C=O), 1713 (C=O), 1663 (C=C), 1496, 1367, 1168 cm^{-1}; $[\alpha]_D^{17}$ +56.9 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.44 (9H, s, ^tBu), 3.33 (1H, dd, *J* 17.8, 4.3 Hz, 3-*H*H), 3.44 (1H, dd, *J* 17.8, 4.1 Hz, 3-H*H*), 3.75 (3H, s, OMe), 4.62 (1H, ddd, *J* 8.5, 4.3, 4.1 Hz, 2-H), 5.60 (1H, d, *J* 8.5 Hz, NH), 6.71 (1H, d, *J* 16.1 Hz, 5-H), 7.38–7.42 (3H, m, ArH), 7.52–7.55 (2H, m, ArH), 7.57 (1H, d, *J* 16.1 Hz, 6-H); δ_C (101 MHz, $CDCl_3$) 28.3 (3×CH_3), 42.4 (CH_2), 49.6 (CH), 52.6 (CH_3), 79.9 (C), 125.6 (CH), 128.4 (2×CH), 129.2 (2×CH), 130.9 (CH), 134.1 (C), 143.9 (CH), 155.6 (C), 172.0 (C), 197.6 (C); *m*/*z* (CI) 334 (MH^+, 9%), 320 (4), 278 (100), 234 (13); HRMS (CI): MH^+, found 334.1653. $C_{18}H_{24}NO_5$ requires 334.1654.

4.12. Methyl (2*S*,5*E*)-2-(*tert*-butoxycarbonylamino)-6-(4′-bromophenyl)-4-oxohex-5-enoate (15)[21f]

The reaction was performed as described above, using (2*S*)-2-(*tert*-butoxycarbonylamino)-4-oxo-5-(trimethylsilanyl)pentanoate (**11**) (0.80 g, 2.52 mmol) and 4-bromobenzaldehyde (0.56 g, 3.0 mmol). Purification by flash chromatography (20% ethyl acetate in petroleum ether) gave methyl (2*S*,5*E*)-2-(*tert*-butoxycarbonyl amino)-6-(4′-bromophenyl)-4-oxohex-5-enoate (**15**) as a white solid (0.48 g, 46%). Mp 78–79 °C; ν_{max} (NaCl) 3437 (NH), 3370, 2978 (CH), 1747 (C=O), 1712 (C=O), 1666 (C=C), 1611, 1488, 1168 cm^{-1};

$[\alpha]_D^{20}$ +42.4 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.44 (9H, s, ^tBu), 3.22 (1H, d, *J* 17.8 Hz, 3-*H*H), 3.41 (1H, d, *J* 17.8 Hz, 3-H*H*), 3.75 (3H, s, OMe), 4.58–4.64 (1H, m, 2-H), 5.56 (1H, d, *J* 8.0 Hz, NH), 6.69 (1H, d, *J* 16.0 Hz, 5-H), 7.40 (2H, d, *J* 8.0 Hz, ArH), 7.46–7.56 (3H, m, 6-H and ArH); δ_C (101 MHz, $CDCl_3$) 28.3 (3×CH_3), 42.6 (CH_2), 49.6 (CH), 52.7 (CH_3), 80.0 (C), 125.2 (C), 126.0 (CH), 129.8 (2×CH), 132.3 (2×CH), 133.0 (C), 142.5 (CH), 155.6 (C), 172.0 (C), 197.5 (C); *m*/*z* (FAB) 412 (MH^+, 22%), 358 (100), 356 (89), 314 (23), 278 (22), 234 (7); HRMS (FAB): MH^+, found 412.0755. $C_{18}H_{23}{}^{79}BrNO_5$ requires 412.0760.

4.13. Methyl (2*S*,5*E*)-2-(*tert*-butoxycarbonylamino)-4-oxo-8-phenyloct-5-enoate (16)[21f]

The reaction was performed as described above, using (2*S*)-2-(*tert*-butoxycarbonylamino)-4-oxo-5-(trimethylsilanyl)pentanoate (**11**) (0.80 g, 2.52 mmol) and 3-phenylpropionaldehyde (0.40 g, 3.0 mmol). Purification by flash chromatography (15% ethyl acetate in petroleum ether) gave methyl (2*S*,5*E*)-2-(*tert*-butoxycarbonylamino)-4-oxo-8-phenyloct-5-enoate (**16**) as a colourless oil (0.46 g, 53%). ν_{max} (NaCl) 3439 (NH), 3371, 3027, 3004, 2978 (CH), 2952, 2930, 2859, 1749 (C=O), 1714 (C=O), 1672, 1630, 1584 (C=C), 1497, 1367, 1167 cm^{-1}; $[\alpha]_D^{19}$ +47.4 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.44 (9H, s, ^tBu), 2.46–2.63 (2H, m, 7-H_2), 2.79 (2H, t, *J* 7.7 Hz, 8-H_2), 3.06 (1H, dd, *J* 18.0, 4.0 Hz, 3-*H*H), 3.30 (1H, dd, *J* 18.0, 4.0 Hz, 3-H*H*), 3.73 (3H, s, OMe), 4.42–4.64 (1H, m, 2-H), 5.53 (1H, br d, *J* 8.8 Hz, NH), 6.10 (1H, dt, *J* 16.0, 1.4 Hz, 5-H), 6.88 (1H, dt, *J* 16.0, 6.8 Hz, 6-H), 7.11–7.37 (5H, m, ArH); δ_C (101 MHz, $CDCl_3$) 28.3 (CH_3), 34.2 (CH_2), 34.3 (CH_2), 41.8 (CH_2), 49.5 (CH), 52.6 (CH_3), 79.9 (C), 126.3 (CH), 128.3 (2×CH), 128.6 (2×CH), 130.3 (CH), 140.5 (C), 147.8 (CH), 155.6 (C), 172.0 (C), 197.7 (C); *m*/*z* (FAB) 362 (MH^+, 14%), 306 (94), 262 (100), 203 (11), 176 (14), 160 (34), 93 (35), 90 (32); HRMS (FAB): MH^+, found 362.1974. $C_{20}H_{28}NO_5$ requires 362.1967.

4.14. (2*S*,5*E*)-2-Amino-4-oxo-6-phenylhex-5-enoic acid hydrochloride (17)

To a solution of methyl (2*S*,5*E*)-2-(*tert*-butoxycarbonylamino)-4-oxo-6-phenylhex-5-enoate (**14**) (0.20 g, 0.60 mmol) in methanol (3.0 mL) was added 6.0 M hydrochloric acid (15 mL) and the reaction mixture heated under reflux for 24 h. The mixture was allowed to cool to room temperature and then extracted with diethyl ether (2×20 mL). The aqueous layer was concentrated in vacuo to give a yellow solid. Recrystallisation from chloroform and methanol gave (2*S*,5*E*)-2-amino-4-oxo-6-phenylhex-5-enoic acid hydrochloride (**17**) as an off-white solid (0.095 g, 62%). Mp 151–153 °C (decomposition); ν_{max} (neat) 3058 (NH), 2976 (CH), 1736 (C=O), 1649 (C=C), 1174, 1126, 854 cm^{-1}; $[\alpha]_D^{24}$ +35.8 (*c* 1.0, MeOH); δ_H (400 MHz, CD_3OD) 3.38–3.58 (2H, m, 3-H_2), 4.36 (1H, dd, *J* 6.6, 4.2 Hz, 2-H), 6.92 (1H, d, *J* 16.3 Hz, 5-H), 7.38–7.50 (3H, m, ArH), 7.63–7.71 (2H, m, ArH), 7.76 (1H, d, *J* 16.3 Hz, 6-H); δ_C (101 MHz, CD_3OD) 40.7 (CH_2), 49.3 (CH), 126.0 (CH), 129.8 (2×CH), 130.2 (2×CH), 132.2 (CH), 135.6 (C), 146.2 (CH), 171.3 (C), 197.6 (C); *m*/*z* (CI) 220 (MH^+, 84%), 205 (100), 203 (61), 159 (53), 147 (34), 113 (21), 97 (20), 81 (50), 69 (61); HRMS (CI): MH^+, found 220.0978. $C_{12}H_{14}NO_3$ requires 220.0974.

4.15. General procedure for the deprotection of enones 14, 15 and 16

To a solution of *N*-Boc-protected amino methyl ester (0.16 mmol) in 1:1 methanol/water (4 mL) was added caesium carbonate (0.21 mmol). The resultant suspension was stirred at room temperature for 48 h. The reaction mixture was concentrated in vacuo and the residue was dissolved in water (10 mL) and acidified to pH 1 with hydrochloric acid (1 M). The aqueous layer was washed with dichloromethane (3×20 mL) and the combined organic layers were concentrated in vacuo. To a solution of the resulting residue (0.16 mmol) in dichloromethane (2 mL) was added trifluoroacetic acid (0.80 mmol) and the reaction mixture was stirred at room temperature under argon for 3 h. The reaction mixture was concentrated in vacuo to give the TFA salts, which were purified by recrystallisation from chloroform and methanol.

*4.15.1. (2S,5E)-2-Amino-4-oxo-6-phenylhex-5-enoic acid trifluoroacetate (**18**).*[21f] Using the general procedure above gave (2*S*,5*E*)-2-amino-4-oxo-6-phenylhex-5-enoic acid trifluoroacetate (**18**) as a white solid (0.13 g, 95%). Mp 112–114 °C (decomposition); ν_{max} (neat) 3028 (NH), 2914 (CH), 1738 (C=O), 1655 (C=C), 1495, 1184, 1134 cm^{-1}; $[\alpha]_D^{19}$ +23.3 (*c* 1.0, MeOH); δ_H (400 MHz, CD_3OD) 3.43 (1H, dd, *J* 18.5, 6.1 Hz, 3-*H*H), 3.48–3.56 (1H, m, 3-H*H*), 4.22–4.28 (1H, m, 2-H), 6.92 (1H, d, *J* 16.2 Hz, 5-H), 7.40–7.48 (3H, m, ArH), 7.62–7.69 (2H, m, ArH), 7.74 (1H, d, *J* 16.2 Hz, 6-H); δ_C (101 MHz, CD_3OD) 40.9 (CH_2), 50.2 (CH), 126.1 (CH), 129.7 (2×CH), 130.2 (2×CH), 132.1 (CH), 135.6 (C), 146.0 (CH), 171.8 (C), 198.0 (C); *m*/*z* (FAB) 220 (MH^+, 42%), 175 (7), 148 (16), 132 (12); HRMS (FAB): MH^+, found 220.0973. $C_{12}H_{14}NO_3$ requires 220.0974.

*4.15.2. (2S,5E)-2-Amino-6-(4′-bromophenyl)-4-oxohex-5-enoic acid trifluoroacetate (**19**).*[21f] Using the general procedure above gave (2*S*,5*E*)-2-amino-6-(4′-bromophenyl)-4-oxohex-5-enoic acid trifluoroacetate (**19**) as a white solid (0.14 g, 93%). Mp 151–152 °C (decomposition); ν_{max} (neat) 3364 (NH), 3061, 1684 (C=O), 1607 (C=C), 1547, 1487, 1397, 1339 cm^{-1}; $[\alpha]_D^{18}$ +55.0 (*c* 0.3, MeOH); δ_H (400 MHz, CD_3OD) 3.23 (1H, dd, *J* 18.8, 9.3 Hz, 3-*H*H), 3.46 (1H, dd, *J* 18.8, 3.4 Hz, 3-H*H*), 3.95 (1H, dd, *J* 9.3, 3.4 Hz, 2-H), 6.91 (1H, d, *J* 16.3 Hz, 5-H), 7.56–7.62 (4H, m, ArH), 7.67 (1H, d, *J* 16.3 Hz, 6-H); δ_C (101 MHz, CD_3OD) 40.9 (CH_2), 50.2 (CH), 126.2 (C), 126.7 (CH), 131.3 (2×CH), 133.4 (2×CH), 134.8 (C), 144.6 (CH), 171.5 (C), 197.7 (C); *m*/*z* (FAB) 298 (MH^+, 31%), 292 (16), 254 (12), 243 (21), 209 (18), 155 (29), 138 (15); HRMS (FAB): MH^+, found 298.0067. $C_{12}H_{13}{}^{79}BrNO_3$ requires 298.0079.

*4.15.3. (2S,5E)-2-Amino-4-oxo-8-phenyloct-5-enoic acid trifluoroacetate (**20**).*[21f] The general two-step procedure described above was used except that a 1:1 acetonitrile/water solution was used for the hydrolysis step. This gave (2*S*,5*E*)-2-amino-4-oxo-8-phenyloct-5-enoic acid trifluoroacetate (**20**) as a white solid (0.10 g, 98%). Mp 94–96 °C (decomposition); ν_{max} (neat) 3161 (NH), 3030, 2918 (CH), 1736 (C=O), 1661 (C=C), 1640, 1604, 1497, 1180 cm^{-1}; $[\alpha]_D^{18}$ +10.2 (*c* 0.3, MeOH); δ_H (400 MHz, CD_3OD) 2.54–2.63 (2H, m, 7-H_2), 2.82 (2H, t, *J* 7.4 Hz, 8-H_2), 3.20 (1H, dd, *J* 18.8, 8.0 Hz, 3-*H*H), 3.28–3.37 (1H, m, 3-H*H*), 4.11 (1H, dd, *J* 8.0, 3.6 Hz, 2-H), 6.17 (1H, dt, *J* 16.0, 1.4 Hz, 5-H), 7.03 (1H, dt, *J* 16.0, 6.9 Hz, 6-H), 7.12–7.31 (5H, m, ArH); δ_C (101 MHz, CD_3OD) 35.3 (CH_2), 35.5 (CH_2), 40.4 (CH_2), 50.5 (CH), 127.3 (CH), 129.5 (2×CH), 129.6 (2×CH), 130.8 (CH), 142.1 (C), 150.5 (CH), 172.5 (C), 198.1 (C); *m*/*z* (FAB) 248 (MH^+, 14%), 247 (2), 203 (8), 176 (12), 160 (8), 132 (4), 100 (1), 90 (3), 76 (4); HRMS (FAB): MH^+, found 248.1289. $C_{14}H_{18}NO_3$ requires 248.1287.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2014.11.059.

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