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Quaternized α,α-Amino Acids via Curtius Rearrangement of Substituted Malonate-Imidazolidinones

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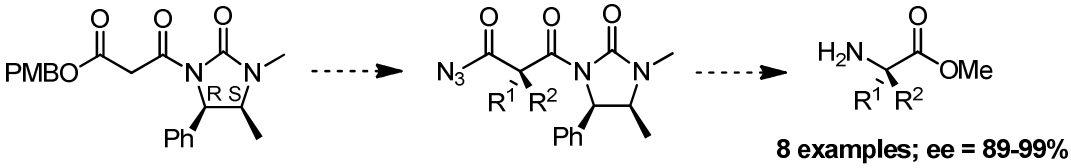


ABSTRACT: An efficient synthesis protocol is presented for accessing quaternized α-amino acids in chiral, non-racemic form via diastereoselective malonate alkylation followed by C- to N-transposition. The key stereodifferentiating step involves a diastereoselective alkylation of an α-monosubstituted malonate-imidazolidinone, which is followed first by a chemoselective malonate PMB ester removal and then a Curtius rearrangement to provide the transposition. The method demonstrates a high product ee (89-99% for eight cases) for quaternizing a range of proteinogenic α-amino acids. The stereogenicity in the targets **5a-i** supports earlier conclusions that the diastereoselective alkylation step proceeds via an α-substituted malonate-imidazolidinone enolate in its *Z*-configuration, with the auxiliary in an s-*trans*$_{C\text{-}N}$ conformation

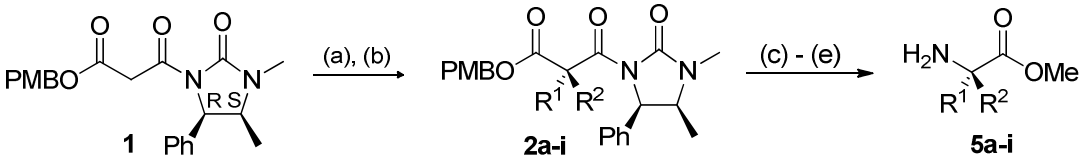
Intense synthetic effort has been directed recently[1] towards developing methodology for accessing acyclic[2] α,α'-disubstituted amino acids in a highly enantioenriched form, in view of their unique stability and ability to impart desirable conformational properties to peptides, particularly in peptidomimetics.[3] Methodologies reported cover the full gamut of

disconnections for the all-important quaternization step, in which carbon-carbon bond-forming quaternization methodologies via either nucleophilic[4, 5] or electrophilic amino acid substrates[6, 7] are most prevalent, and carbon-nitrogen quaternizations via electrophilic[8] and nucleophilic[9] nitrogen sources are also prominent. By comparison, effective radical,[10] pericyclic-type,[11] and enantioselective insertion[12] methodologies are far less common. However, in spite of all these advances, many of the methods do not demonstrate direct application to quaternizing a range of proteinogenic amino acids. We herein report on a strategy involving Curtius rearrangement of suitably functionalized α,α'-disubstituted malonate imidazolidinones that provides access to a range of proteinogenic amino acids in high ee and good overall yield.

Successful strategies for using malonate as a template for elaboration into quaternized amino acids in high ee via C- to N- transposition have involved diastereoselective alkylation[13a] incorporating menthol as a chiral auxiliary into one of the carboxyl groups (albeit with modest diastereoselectivity and limited scope in the products obtained), phase-transfer catalysed enantioselective alkylation[14] and enzyme-promoted desymmetrization[15] strategies. We have recently described[13b] a highly diastereoselective alkylation of malonate-imidazolidinones to afford all-C quaternized products **2a-i** (Scheme 1), and from the outset a key issue regarding extending the work to a Curtius strategy for accessing quaternized α, α'-amino acids centred on differentiation[14,16] of the two carboxyl group functionalities post alkylation. Eventually, this was satisfactorily achieved by using a PMB ester on the non-auxiliary group, in which chemoselective deprotection (of **2a-i**) to the half acid **3a-i** could be achieved using TFA in DCM at 0 °C without decarboxylation. Thereafter, the half acid was committed to a standard Curtius sequence using diphenylphosphoryl azide (DPPA) for acyl azide generation to afford auxiliary-amines **4a-i** following thermal rearrangement and acid

hydrolysis, with the auxiliary still attached. Auxiliary deprotection in the final step via methanolysis (NaOMe) then afforded quaternized amino acid esters **5a-i** as shown in Scheme 1.

Scheme 1. Malonate-imidazolidinone alkylation / Curtius sequence for quaternized α,α–amino acid esters 5a-i

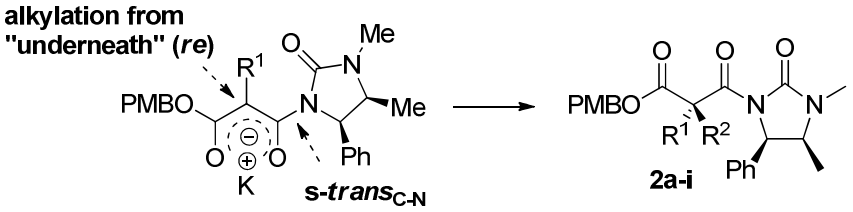


(a) KHMDS (1.2 eq), THF, -78 °C; R^1X (1.5 eq) to rt or Δ
(b) KHMDS (1.2 eq), THF, -78 °C; R^2X (1.5 eq) to rt or Δ to afford **2a-i**; > 80% for the two steps
(c) TFA, anisole, DCM, rt to afford acids **3a-i**
(d) DPPA, NEt_3, THF; Δ, CH_3CN; aq HCl to afford transposed aux-amines **4a-i**; 62-83% from **2a-i**
(e) NaOMe, MeOH, rt to afford **5a-i**; 68-97% from **4a-i**

Specifically, the sequence begins with sequential double alkylation of malonate-imidazolidinone **1** according to our earlier communication,[13b] in which **1** was readily prepared by a sequential double DCC coupling of malonic acid with first PMBOH followed by the auxiliary in around 85% yield for each step (see the Experimental Section). Following the double alkylation with KHMDS (1.2 eq), the pivotal all-carbon quaternized malonates **2a-i** were obtained in high diastereoselectivity (de = 86 - > 99%) after column chromatography as evidenced by HPLC analysis on a C18 column. Their ^{1}H NMR spectra according to reliable markers that consistently allowed facile identification of the diastereomeric ratio (the auxiliary benzylic H and Me doublets together with the N-Me singlet) indicated a virtually pure diastereomer in each case. The diastereomers eluted together and while very small amounts of the minor diastereomer may have been lost during fraction collection, the high des observed from the HPLC data we consider to closely reflect the de in the reaction itself. An overall yield for the two alkylation steps was in excess of 80 % overall, while the R^2 (second) group could only be introduced as Me, allyl, propargyl or benzyl in keeping with the

need to use a reactive S_N2 electrophile. The sense of diastereoselectivity was based on our earlier findings[13b] that reaction proceeds via a (*Z*)-, s-*trans*$_{C\text{-}N}$ malonate-imidazolidinone enolate intermediate in which R^2 is introduced *anti* to the face bearing the bulky groups on the auxiliary. This mechanistic view, in conjunction with the known retention of configuration in the Curtius step, was corroborated by optical rotation data for **5a**, **5b**, **5e**, and **5g** in which the signs of rotation were all in agreement with those in the literature (see the Experimental), while the other products were obtained as new compounds. Figure 1 presents a transition state model that accommodates these ideas.

Figure 1. Proposed transition-state model for quaternization.



Thereafter, compounds **2a-i** were deprotected with TFA in DCM at rt to afford acid products **3a-i**, which could be cleanly isolated via an acid/base extraction without recourse to chromatography. Conversion of the half acid to its acyl azide using diphenylphosphoryl azide (DPPA) with triethylamine in THF followed by a Curtius rearrangement in refluxing acetonitrile achieved a clean conversion to the isocyanate, which was hydrolysed to auxiliary-amines **4a-i** with aqueous mineral acid. The amine product could also be isolated in high purity using an acid/base extraction, also without the need for chromatography and in an overall yield for the four steps from **2a-i** of around 70%. Finally, auxiliary deprotection with sodium methoxide in methanol furnished the quaternized targets **5a-i** in around 75% yield after column chromatography, with virtually quantitative recovery of the auxiliary (on a small scale). Amino acid esters **5a-i** were quite stable, were relatively non-polar on chromatography and generally didn't require *N*-protection for characterisation unless to introduce a UV-active chromophore for HPLC ee evaluation (via *N*-benzamide formation). Table 1 reveals the range

of amino acids synthesized. The high enantioselectivities of quaternization were extremely pleasing, and according to chiral HPLC data closely correlated with the de of the corresponding dialkylated malonate-imidazolidinones **2a-i**. Furthermore, the range of ees shown in Table 1 agreed with earlier work in that ees generally increased with the steric bulk of the R^1 group - lowest ee with allyl (**5b**; 89%); highest with tryptophan (**5i**; 99%). By way of HPLC standards, racemates for **2a**, **2b** and **2e** were prepared via alkylation of the respective amino acid *p*-bromophenyl imine according to a literature procedure,[17] modifying the base (from KOH to NaH for **2a** and **2b**, and KHMDS for **2e**). For **5a**, owing to asymmetry in the HPLC trace, the ee (reported as 99%) is probably closer to its de value (96%).

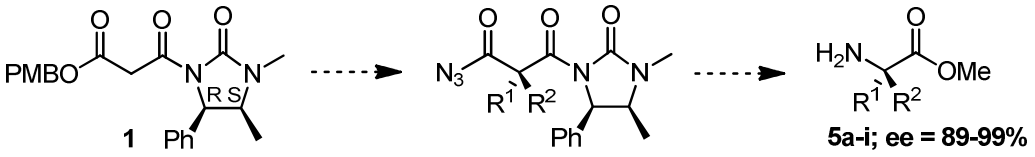
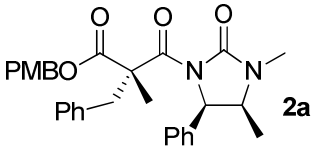
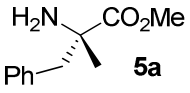
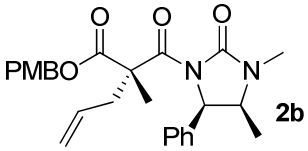
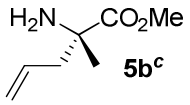
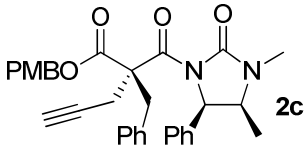
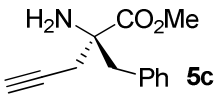
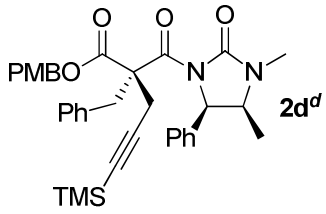
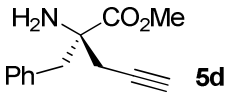
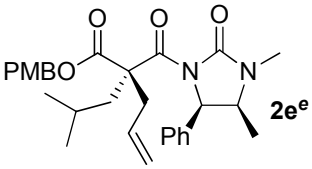
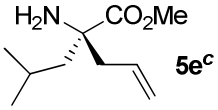
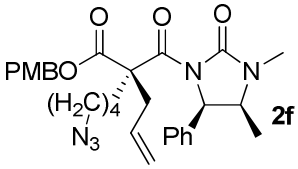
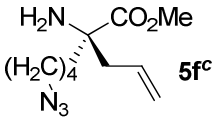
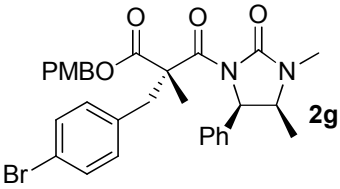
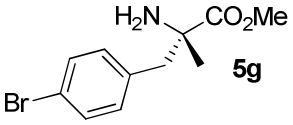
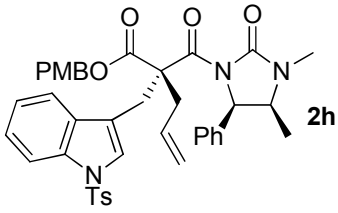
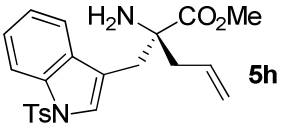
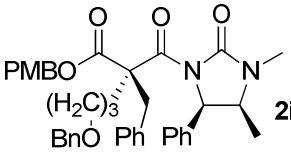
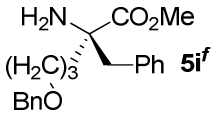


Table 1. Ees of Quaternized α-Amino Acids **5a-i**

Entry	Product 2	Product 5	de of 2[a]	ee of 5[b]
1	 **2a**	 **5a**	96	99
2	 **2b**	 **5b**[c]	86	89
3	 **2c**	 **5c**	67	70

4	 **2d**[d]	 **5d**	92	92
5	 **2e**[e]	 **5e**[c]	97	99
6	 **2f**	 **5f**[c]	99	98
7	 **2g**	 **5g**	99	98
8	 **2h**	 **5h**	> 99	> 99
9	 **2i**	 **5i**[f]	93	90

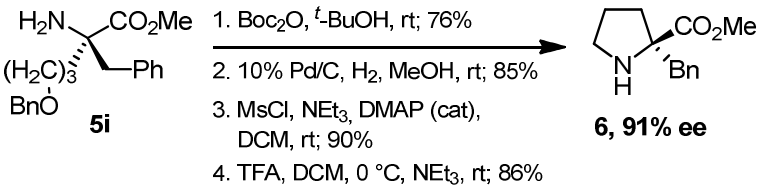
[a]Measured by HPLC on a C18 column. [b]Measured using chiral HPLC on a Chiralcel OD or AD column. [c]*N*-benzamide used for the HPLC determination. [d]Using 3-bromo-1-trimethylsilylpropyne to introduce the R^2 group (The TMS group removed subsequently by TBAF). [e]Isobutyl group introduced as the R^1 group at the malonate level. [f]ee evaluated via its *N*-Boc derivative.

The R groups were chosen to cover a range of commonly employed amino acids in synthesis, including Ala and Phe (**5a-d, g, i**), Leu (**5e**), Lys (**5f**), Trp (**5h**) and Pro (**5i**), the latter derived

from **5i** via a short sequence as shown in Scheme 2. Using the (4*R*, 5*S*) auxiliary (numbering based on the free auxiliary) as shown in Scheme 1 meant that the quaternizing group R^2 always replaced the H of an (*S*)-α-amino acid. The outcome of **5c** is interesting in that using R^1 as propargyl delivered a lower-than-normal ee of 70% (67% de for **2c**). This was in agreement with our earlier findings[13b] that the steric size of the R^1 group controls s-*trans* to s-*cis* auxiliary interconversion. Propargyl is presumably on the cusp between ethyl and methyl, the latter being too small to inhibit auxiliary conformation interconversion (the de was close to zero for R^1 = Me, while about 90% with Et[13b]). Reversal of the order of introduction of the two groups (benzyl and propargyl) led to complications with R^2 as propargyl, probably due to the acidity of the terminal alkyne hydrogen. This could be resolved by using 3-bromo-1-trimethylsilylpropyne as the second electrophile, which following desilylation with TBAF (quantitative yield) and committing to the Curtius sequence afforded **5d** in high ee (92%). Similarly, the quaternized leucine derivative **5e** (99% ee) could be accessed from **2e**, in which the isobutyl group was installed into diethyl malonate first. Hydrolysing the latter to the diacid, carrying out the double DCC coupling to afford the malonate-imidazolidinone with R^1 as an isobutyl group already installed, and carrying out the second alkylation then gave access to **2e**. Azide **5f** was obtained from **2f** using $Br(CH_2)_4N_3$[18] as the electrophile for introducing the R^1 group in the first alkylation. The ee of **5f** was determined via its *N*-benzamide, which could be converted into N^2-Bz, N^6-Boc α-allyllysine methyl ester via a Staudinger / *N*-Boc protection sequence on the terminal azide (see the Supplementary Information). Both **5f** and the protected lysine derivative were obtained in an excellent ee of 98%. Product **5g** containing a *p*-bromobenzyl / methyl combination is the enantiomer of a key intermediate in the synthesis of the LFA-1 antagonist BIRT-377,[15c,19] and was obtained in an ee of 98% ee, which compares extremely favourably to other reported stereoselectivities, The actual enantiomer in question could in principle be easily accessed by simply using the

(4*S*, 5*R*) auxiliary antipode. Similarly, the tryptophan derivative **5h**, using *N*-tosyl-3-chloromethylindole[20] in the first alkylation en route to **2h**, was produced essentially enantiopure (ee > 99%) as its N_{ind}-tosyl derivative - the use of sulfonamide as protecting group avoided complications using N_{ind}-Boc in the TFA deprotection step. Finally, product **5i** (90% ee), containing a terminal benzyloxy group, could be converted into quaternized α–benzylproline methyl ester **6** as its (*R*)-enantiomer in 91% ee via a straightforward sequence as shown in Scheme 2 below. One quaternized amino acid that couldn't be accessed, however, was that of serine. Several attempts to install a C1 moiety, either as a first or second R group and involving a range of hydroxymethylene C1 surrogates such as CH_2SPh, CH_2TMS, CH_2OBn or $CH_2O(CH_2)_2TMS$, introduced via either direct alkylation with the halide or via thiophenol Michael addition[21] to the malonate exo-methylene derivative, all failed. An alternative viable methodology developed in the group (using malonate-imidazolidinones) for accessing quaternized serines[5b] will be reported elsewhere.

Scheme 2. Synthesis of (*R*)-α-benzylproline Me ester 6 from 5i



CONCLUSION

In summary, this study has significantly improved the scope[13a] of accessing quaternised α-amino acids in high ee via a diastereoselective auxiliary-controlled malonate alkylation / Curtius rearrangement sequence. Based on the results, the method would appear to offer access to most of the proteinogenic amino acids (serine excluded) in high ee, whose stereogenicity can be predicted by a transition-state model.

EXPERIMENTAL SECTION

Unless otherwise specified, all reagents were purchased from commercial sources and used without further purification. THF was freshly distilled over sodium wire and benzophenone. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Mercury 300 MHz (75.5 MHz for ^{13}C) or a Bruker 400 MHz (101 MHz for ^{13}C) instrument. All spectral data was acquired at 295 K. Chemical shifts are reported in parts per million (ppm, δ), downfield from tetramethylsilane (TMS, δ = 0.00 ppm) and are referenced to residual solvent ($CDCl_3$, δ = 7.26 ppm (^{1}H) and 77.16 ppm (^{13}C)). Coupling constants (*J*) are reported in Hertz (Hz). The multiplicity abbreviations used are: br broad, s singlet, d doublet, t triplet, q quartet, m multiplet. Infrared (IR) spectra were recorded on a Perkin Elmer Spectrum 100 FT-IR Spectrometer. High-resolution mass-spectra were obtained from the University of Stellenbosch Mass Spectrometry Service and recorded in electrospray positive mode with a time-of-flight analyser system on a Waters Synapt G2 machine. Thin layer chromatography was carried out on Merck silica gel $60F_{254}$ pre-coated aluminium foil sheets and were visualised using UV light (254 nm). Column chromatography was carried out using silica gel 60 (Merck 7734), eluting with the specified solvent system. The diastereomeric ratios of compounds **2a-i** were determined by HPLC on an Agilent 1220 Series using a Zorbax Eclipse Plus C18 (150 x4.6 mm) column, while the ees of quaternized amino acid esters **5a-i** were determined by HPLC on an Agilent 1220 Series using Daicel Chiralcel OD (250 × 4.6 mm) or Daicel Chiralpak AD (250 × 4.6 mm) column. The full details of the HPLC solvents used and the retention times obtained are given in the SI. Racemates of **5a**, **5b** and **5e** for HPLC comparison purposes were prepared via alkylation of the *p*-bromphenyl imine of the respective amino acid Me ester (NaH for **5a** and **5b**, and KHMDS for **5e**) according to a literature procedure.[17] Optical rotations were obtained using a Perkin Elmer 343 polarimeter at λ = 589 nm and 20 ºC. The concentration *c* refers to g/100mL.

Synthesis of 4-methoxybenzyl-3-((4*S*,5*R*)-3,4-dimethyl-2-oxo-5-phenylimidazolidin-1-yl)-3-oxopropanoate 1

To a cooled solution of malonic acid (15.00 g, 0.144 mol) and *p*-methoxybenzyl alcohol (17.90 mL, 0.144 mol, 1 eq) in acetonitrile (350 ml) was added a solution of DCC (29.70 g, 0.144 mol, 1 eq) in acetonitrile (150 ml) via a dropping funnel over a period of 30 min, whilst stirring vigorously. The cooling bath was then removed and the reaction mixture was left to stir for 1 h at rt after which time the solid urea precipitate was removed by filtration through a pad of Celite® and the filtrate evaporated. The residue was taken up in ethyl acetate (250 mL) and the organic layer extracted with saturated aqueous sodium bicarbonate solution (2 x 200 mL). The combined aqueous extracts were washed once with ethyl acetate (100 mL), acidified to pH 3 with 3M HCl and then extracted with ethyl acetate (1 x 300 and 2 x 150 mL). The organic extracts were dried over anhydrous $MgSO_4$, filtered and evaporated to yield mono-PMB malonic acid (26.80 g, 0.120 mol, 86%) as a light-yellow liquid.

Mono-PMB malonic acid (6.00 g, 26.8 mmol, 1 eq) and (4*R*,5*S*)-1,5-dimethyl-4-phenylimidazolidin-2-one (5.10 g, 26.8 mol, 1 eq) were dissolved in dichloromethane (100 mL) and stirred at 0 ºC. A solution of DCC (6.63 g, 32.1 mol, 1.2 eq) and HOBt (0.721 g, 5.3 mmol, 20 mol %) in dichloromethane (50 mL) was gradually added to the mixture via a pressure-equalizing dropping funnel.

Once addition was complete, the cooling bath was removed. The reaction was followed by TLC, which indicated completion within 3 h at room temperature after which time it was filtered through Celite®, the solvent was evaporated and the resultant residue purified by column chromatography with ethyl acetate/hexane (30/70). The product **1** (9.03 g, 22.8 mmol, 85%) was obtained as a thick, clear gum.

$[\alpha]_D^{20}$ = –30.3º, (*c* = 1, CH_2Cl_2); IR: ν_{max} (cm^{-1}) 3067, 2961, 1732, 1687; ^1H NMR (400 MHz, $CDCl_3$) δ 7.31–7.19 (m, 5H), 7.17–7.08 (m, 2H), 6.86 (d, *J* = 8.7 Hz, 2H), 5.28 (d, *J* = 8.7

Hz, 1H), 5.09 (s, 2H), 3.99 (m 2H), 3.87 (dq, *J* = 8.7, 6.6 Hz, 1H), 3.78 (s, 3H), 2.78 (s, 3H), 0.76 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.6, 164.9, 159.8, 155.6, 136.1, 130.2, 128.6, 128.2, 127.9, 127.2, 114.1, 66.9, 59.5, 55.4, 54.2, 43.5, 28.3, 15.1; HRMS (ES) *m/z*: $[M + H]^+$ Calcd for $C_{22}H_{25}N_2O_5$ 397.1763; Found 397.1748.

General Procedure A: synthesis of α, α'-disubstituted auxiliary malonates (2a-i)

A solution of **1** (1 eq) in THF (0.1 M) was cooled to −78 ºC to which was added KHMDS in toluene (0.5 M, 1.2 eq) dropwise. Stirring at this temperature was continued for a further 30 min after which time the electrophile in THF (1.5 eq) was added. The reaction mixture was slowly warmed to rt and stirred for a further 18 h at this temperature. For **2h** the reaction mixture was stirred for an extra 1 h at 40 ºC, while for **2f** and **2i** the reaction mixture was stirred for the 18 h at 60 ºC. The mixture was then quenched with saturated aqueous ammonium chloride solution (*ca*. ½ reaction vol.) and extracted three times with EtOAc (3 x reaction vol.). The combined organic extracts were dried over anhydrous $MgSO_4$ and evaporated to give the crude product, which was chromatographed using EtOAc/hexanes mixtures as eluents to afford the monoalkylated derivatives of **1**.

The mono-alkylated auxiliary malonate (1 eq.) in THF (0.1 M) in THF was cooled to −78 ºC and KHMDS in toluene (0.5 M, 1.2 eq.) added. After 30 min the electrophile (1.5 eq. in THF) was added dropwise. The reaction mixture was slowly warmed to rt and stirred for a further 18 h (for **2h** the reaction mixture was then warmed to 30 ºC for an additional 5 h). The solution was then quenched with saturated aqueous ammonium chloride solution (*ca*. ½ reaction vol.) and extracted three times with EtOAc (3 x reaction vol.). The combined organic extracts were dried over anhydrous $MgSO_4$ and evaporated to give the crude product which was chromatographed using EtOAc/hexanes (20/80) to give **2a-i**.

*4-Methoxybenzyl (S)-2-benzyl-3-((4S,5R)-3,4-dimethyl-2-oxo-5-phenylimidazolidin-1-yl)-2-methyl-3-oxopropanoate (**2a**)*

Prepared according to general procedure A from **1** (0.900 g, 2.27 mmol), using KHMDS (0.5 M, 5.45 mL, 2.73 mmol) and benzyl bromide (0.40 mL, 3.40 mmol) to give 4-methoxybenzyl 2-benzyl-3-((4*S*,5*R*)-3,4-dimethyl-2-oxo-5-phenylimidazolidin-1-yl)-3-oxopropanoate (1.05 g, 2.16 mmol, 95%). A portion of this (0.900 g, 1.85 mmol) was then subjected to the second alkylation using KHMDS (0.5 M, 4.44 mL, 2.22 mmol) and methyl iodide (0.18 mL, 2.90 mmol) to afford **2a** as a colourless gum (0.889 g, 96%) in a de of 96%.

$[\alpha]_D^{20}$ = –45.8º, (*c* = 1.0, CH_2Cl_2); IR (ν_{max}/cm^{-1}) 3008, 2955, 1722, 1669; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25–7.14 (m, 8H), 7.12–7.07 (m, 2H), 7.04–6.99 (m, 2H), 6.87–6.82 (m, 2H), 5.13 (d, *J* = 8.5 Hz, 1H), 5.05 (d, *J* = 11.7 Hz, 1H), 4.93 (d, *J* = 11.7 Hz, 1H), 3.81 (s, 3H), 3.77 (dq, *J* = 8.5, 6.4 Hz, 1H), 3.37 (d, *J* = 14.8 Hz, 1H), 3.33 (d, *J* = 14.8 Hz, 1H) 2.75 (s, 3H), 1.46 (s, 3H), 0.73 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.4, 169.8, 159.7, 155.3, 137.2, 136.5, 130.6, 130.5, 128.5, 128.2, 128.1, 128.0, 126.9, 126.8, 113.9, 66.6, 60.5, 56.5, 55.5, 54.4, 41.7, 28.2, 22.1, 15.1; HRMS (ESI$^+$) *m/z*: $[M + H]^+$ Calcd for $C_{30}H_{33}N_2O_5$ 501.2384; Found 501.2390.

4-Methoxybenzyl (S)-2-((4S,5R)-3,4-dimethyl-2-oxo-5-phenylimidazolidine-1-carbonyl)-2-methylpent-4-enoate ***(2b)***

Prepared according to general procedure A from **1** (0.900 g, 2.27 mmol), using KHMDS (0.5 M, 5.45 mL, 2.73 mmol) and allyl bromide 0.30 mL, 3.47 mmol) to give 4-methoxybenzyl 2-((4*S*, 5*R*)-3,4-dimethyl-2-oxo-5-phenylimidazolidine-1-carbonyl)pent-4-enoate (0.961 g, 2.20 mmol, 97%). A portion of this (0.820 g, 1.88 mmol), was then subjected to the second alkylation using KHMDS (0.5 M, 4.50 mL, 2.25 mmol) and methyl iodide (0.18 mL, 2.90 mmol) to afford **2b** as a colourless viscous oil (0.762 g, 90%) in a de of 86%.

$[\alpha]_D^{20}$ = –46.2º, (*c* = 1.0, CH_2Cl_2); IR (ν_{max}/cm^{-1}) 3063, 2937, 1723, 1676; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31–7.26 (m, 2H), 7.25–7.16 (m, 3H), 7.07–7.02 (m, 2H), 6.91–6.85 (m, 2H), 5.71 (m, 1H), 5.23 (d, *J* = 8.6 Hz, 1H), 5.13 (d, *J* = 11.9 Hz, 1H), 5.05 (d, *J* = 11.9 Hz,

1H), 5.02–4.96 (m, 2H), 3.81 (s, 3H), 3.79 (dq, *J* = 8.6, 6.6 Hz, 1H), 2.73 (s, 3H), 2.72–2.68 (m, 2H), 1.46 (s, 3H), 0.73 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.3, 170.2, 159.7, 155.2, 136.6, 133.8, 130.5, 128.6, 128.4, 128.1, 126.9, 118.2, 114.0, 66.5, 60.4, 55.5, 55.2, 54.3, 40.7, 28.2, 21.4, 15.1; HRMS (ESI^+) *m/z*: $[M + H]^+$ Calcd for $C_{26}H_{31}N_2O_5$ 451.2233; Found 451.2233.

4-Methoxybenzyl (R)-2-benzyl-2-((4S,5R)-3,4-dimethyl-2-oxo-5-phenylimidazolidine-1-carbonyl)pent-4-ynoate ***(2c)***

Prepared according to general procedure A from **1** (0.900 g, 2.27 mmol) using KHMDS (0.5 M, 5.45 mL, 2.73 mmol) propargyl bromide (0.37 ml, 80%, 3.43 mmol) to give 4-methoxybenzyl 2-((4*S*, 5*R*)-3,4-dimethyl-2-oxo-5-phenylimidazolidine-1-carbonyl)pent-4-ynoate (0.880 g, 2.02 mmol, 89%). This was then subjected to the second alkylation using KHMDS (0.5 M, 4.88 mL, 2.44 mmol) and benzyl bromide (0.36 mL, 3.00 mmol) to afford **2c** as a colourless gum (0.770 g, 73%) in a de of 67%.

IR (ν_{max}/cm^{-1}) 3281, 3065, 2940, 2258, 1727, 1675; ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 7.31–7.00 (m, 10H), 6.99–6.91 (m, 2H), 6.88–6.80 (m, 2H), 5.29 (d, *J* = 8.6 Hz, 1H), 4.99 (d, *J* = 11.7 Hz, 1H), 4.93 (d, *J* = 11.7 Hz, 1H), 3.86 (dq, *J* = 8.6, 6.6 Hz, 1H), 3.80 (s, 3H), 3.42 (br s, 2H), 3.13 (dd, *J* = 18.0, 2.7 Hz 1H), 2.83 (dd, *J* = 18.0, 2.7 Hz, 1H), 2.76 (s, 3H), 2.12 (t, *J* = 2.7 Hz, 1H), 0.74 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) *δ* 169.5, 167.9, 159.6, 155.1, 136.1, 136.0, 130.5, 128.3, 128.0, 127.9, 127.7, 127.2, 126.8, 126.7, 113.7, 79.9, 71.9, 66.6, 60.7, 59.1, 55.3, 54.2, 39.2, 28.1, 23.0, 14.9; HRMS (ESI^+) *m/z*: $[M + H]^+$ Calcd. for $C_{32}H_{33}N_2O_5$ 525.2384; Found 525.2389.

4-Methoxybenzyl (R)-2-benzyl-2-((4S,5R)-3,4-dimethyl-2-oxo-5-phenylimidazolidine-1-carbonyl)-5-(trimethylsilyl)pent-4-ynoate ***(2d)***

Prepared according to general procedure from **1** (0.900 g, 2.27 mmol), KHMDS (0.5 M, 5.45 mL, 2.73 mmol) and benzyl bromide (0.40 mL, 3.36 mmol) to give 4-methoxybenzyl 2-

benzyl-3-((4*S*, 5*R*)-3,4-dimethyl-2-oxo-5-phenylimidazolidin-1-yl)-3-oxopropanoate (1.05 g, 2.16 mmol, 95%). A portion of this (0.900 g, 1.85 mmol) was then subjected to the second alkylation using KHMDS (0.5 M, 4.44 mL, 2.22 mmol) and 3-bromo-1-(trimethylsilyl)-1-propyne (527 mg, 2.78 mmol) to afford **2d** as a colourless gum (0.800 g, 73%) in a de of 92%.

$[\alpha]_D^{20} = -57.5°$, (c = 1.0, CH_2Cl_2); IR (ν_{max}/cm^{-1}) 3060, 3024, 2840, 2247, 1727, 1685; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34–7.07 (m, 12H), 6.95–6.84 (m, 2 H), 5.28 (d, J = 8.7 Hz, 1H), 5.08 (d, J = 11.7 Hz, 1H), 4.91 (d, J = 11.7 Hz, 1H), 3.85 (s, 3H), 3.85–3.74 (m, 1H), 3.60 (d, J = 14.1 Hz, 1H) 3.52 (d, J = 14.1 Hz, 1 H), 3.34 (d, J = 17.7, 1H), 2.88 (d, J = 17.7, 1H), 2.80 (s, 3H), 0.77 (d, J = 6.6 Hz, 3H), 0.06 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.8, 167.7, 159.6, 155.2, 136.7, 136.3, 130.5, 130.3, 128.4, 128.1, 128.0, 128.0, 127.1, 126.9, 113.8, 102.2, 89.4, 66.5, 60.4, 59.4, 55.4, 54.4, 38.7, 28.1, 24.9, 15.0, 0.0; HRMS (ESI$^+$) *m/z*: $[M + H]^+$ Calcd. for $C_{35}H_{41}N_2O_5Si$ 597.2779; Found 597.2781.

Compound **2d** could be desilylated in quantitative yield using TBAF in THF, in preparation for the Curtius sequence.

4-Methoxybenzyl (R)-2-((4S,5R)-3,4-dimethyl-2-oxo-5-phenylimidazolidine-1-carbonyl)-2-isobutylpent-4-enoate ***(2e)***

In the case of the mono-alkylated precursor for **2e** the first substituent was introduced at the malonate level via a sequence involving malonate alkylation (NaH, DMF) with 1-bromo-2-methylpropane, double ester hydrolysis (KOH, EtOH), followed by sequential DCC coupling with PMBOH and auxiliary respectively. Thereafter, general procedure A using 4-methoxybenzyl 2-((4*S*, 5*R*)-3,4-dimethyl-2-oxo-5-phenylimidazolidine-1-carbonyl)-4-methylpentanoate (0.450 g, 0.996 mmol), KHMDS (0.5 M, 2.40 mL, 1.20 mmol) and allyl bromide (0.13 mL, 1.50 mmol) gave **2e** as a viscous oil (0.402 g, 82%) in a de of 97%.

$[\alpha]_D^{20}$ = –9.4º, (*c* = 1.0, CH_2Cl_2); IR (ν_{max}/cm^{-1}) 3067, 2957, 1730, 1672, 1613; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32–7.7.25 (m, 2H), 7.22–7.10 (m, 3H), 7.07–6.98 (m, 2H), 6.92–6.83 (m, 2H), 5.55–5.5.35 (m, 1H), 5.20 (d, *J* = 8.4 Hz, 1H), 5.09 (d, *J* = 12.0 Hz, 1H), 5.03 (d, *J* = 12.0 Hz, 1H), 4.99–4.83 (m, 2H), 3.81 (s, 3H), 3.81–3.72 (m, 1H), 2.80–2.72 (m, 1H), 2.73 (s, 3H), 2.06 (dd, *J* = 14.4, 4.2 Hz, 1H), 1.93-1.78 (m, 1H), 1.76–1.56 (m, 2H), 0.90 (d, *J* = 6.6 Hz, 3H), 0.80 (d, *J* = 6.6 Hz, 3H), 0.72 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) *δ* 171.4, 170.2, 159.7, 155.2, 136.5, 133.6, 130.6, 128.4, 128.3, 128.0, 127.1, 118.1, 114.0, 66.5, 60.8, 58.3, 55.5, 54.3, 41.9, 39.1, 28.2, 25.1, 24.1, 23.5, 15.1; HRMS (ESI^+) *m/z*: $[M + H]^+$ Calcd for $C_{29}H_{37}N_2O_5$ 493.2697; Found 493.2698.

4-Methoxybenzyl (R)-2-allyl-6-azido-2-((4S,5R)-3,4-dimethyl-2-oxo-5-phenylimidazolidine-1-carbonyl)hexanoate ***(2f)***

Prepared according to general procedure A from **1** (0.900 g, 2.27 mmol) using KHMDS (0.5 M, 5.45 mL, 2.73 mmol), 1-azido-4-bromobutane[18] (0.603 g, 3.40 mmol) and TBAI (0.369 g, 1.14 mmol) to give 4-methoxybenzyl 6-azido-2-((4S,5R)-3,4-dimethyl-2-oxo-5-phenylimidazolidine-1-carbonyl)hexanoate (0.951 g, 1.92 mmol, 85%) In this case, the reaction mixture had to be warmed to 60 ºC to achieve full conversion. A portion of this (0.930 g, 1.89 mmol), was then subjected to the second alkylation using KHMDS (0.5 M, 4.52 mL, 2.26 mmol) and allyl bromide (0.25 mL, 2.89 mmol) to afford **2f** as a viscous oil (0.960 g, 95%) in a de of 99%.

$[\alpha]_D^{20}$ = –31.2º, (*c* = 1.0, $CHCl_3$); IR (ν_{max}/cm^{-1}) 3071, 2936, 2094, 1728, 1672, 1613; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33–7.26 (m, 2H), 7.25–7.15 (m, 3H), 7.10–7.03 (m, 2H), 6.93–6.84 (m, 2H), 5.44–5.28 (m, 1H), 5.26 (d, *J* = 8.7 Hz, 1H), 5.11 (d, *J* = 12.0 Hz, 1H), 5.04 (d, *J* = 12.0 Hz, 1H), 5.00–4.84 (m, 2H), 3.81 (m, 3H), 3.80 (dq, *J* = 8.7, 6.6 Hz, 1H), 3.26–3.12 (m, 2H), 3.02–2.91 (m, 1H), 2.79–2.67 (m, 4H), 2.03–1.02 (m, 6H), 0.74 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) *δ* 171.3, 169.5, 159.8, 155.2, 136.5, 133.0, 130.6,

128.5, 128.2, 128.1, 127.2, 118.4, 114.0, 66.5, 60.5, 58.2, 55.5, 54.2, 51.2, 38.1, 32.9, 29.2, 28.2, 21.4, 15.1; HRMS (ESI^+) *m/z*: $[M + H]^+$ Calcd for $C_{29}H_{36}N_5O_5$ 534.2711; Found 534.2721.

4-Methoxybenzyl (S)-2-(4-bromobenzyl)-3-((4S,5R)-3,4-dimethyl-2-oxo-5-phenylimidazolidin-1-yl)-2-methyl-3-oxopropanoate ***(2g)***

Prepared according to general procedure A from **1** (0.900 g, 2.27 mmol), using KHMDS (0.5 M, 5.45 ml, 2.73 mmol) and *p*-bromobenzyl bromide (0.843 g, 3.40 mmol). to give 4-methoxybenzyl 2-(4-bromobenzyl)-3-((4*S*, 5*R*)-3,4-dimethyl-2-oxo-5-phenylimidazolidin-1-yl)-3-oxopropanoate (1.260 g, 2.23 mmol, 98%). A portion of this (1.200 g, 2.13 mmol), was then subjected to the second alkylation using KHMDS (0.5 M, 5.10 mL, 2.55 mmol) and methyl iodide (0.40 mL, 6.42 mmol) to afford **2g** (1.100 g, 89%) as a colourless gum in a de of 99%.

$[\alpha]_D^{20}$ = –36.5º, (*c* = 1.0, CH_2Cl_2); IR (ν_{max}/cm^{-1}) 2936, 1724, 1676; ^1H NMR (300 MHz, $CDCl_3$) δ 7.35–7.28 (m, 2H), 7.26–7.18 (m, 3H), 7.18–7.11 (m, 2H) 7.06–6.93 (m, 4H), 6.90–6.82 (m, 2H), 5.18 (d, *J* = 8.7 Hz, 1H), 5.03 (d, *J* = 11.9 Hz, 1H), 4.88 (d, *J* = 11.9 Hz, 1H), 3.82 (s, 3H), 3.77 (dq, *J* = 8.7, 6.6 Hz, 1H), 3.33 (d, *J* = 13.8 Hz, 1H), 3.18 (d, *J* = 13.8 Hz, 1H), 2.74 (s, 3H), 1.48 (s, 3H), 0.74 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.9, 169.7, 159.7, 155.1, 136.4, 136.2, 132.3, 131.1, 130.5, 128.6, 128.1, 127.9, 126.9, 120.8, 113.9, 66.6, 60.4, 56.5, 55.4, 54.3, 41.4, 28.2, 22.0, 15.0; HRMS (ESI^+) *m/z*: $[M + H]^+$ Calcd. for $C_{30}H_{32}N_2O_5Br^{79}$ 579.1489; Found 579.1475.

*4-Methoxybenzyl (S)-2-((4S,5R)-3,4-dimethyl-2-oxo-5-phenylimidazolidine-1-carbonyl)-2-((1-tosyl-1H-indol-3-yl)methyl)pent-4-enoate (**2h**)*

Prepared according to general procedure A from **1** (0.500 g, 1.26 mmol), using KHMDS (0.5 M, 3.8 mL, 1.90 mmol) and 3-(chloromethyl)-1-tosyl-1*H*-indole[19] (0.525 g, 1.64 mmol, 1.3 eq) to give 4-methoxybenzyl 2-((4S,5R)-3,4-dimethyl-2-oxo-5-phenylimidazolidine-1-

carbonyl)-2-((1-tosyl-1H-indol-3-yl)methyl)pent-4-enoate (0.750 g, 1.10 mmol, 87%). This was then subjected to the second alkylation using KHMDS (0.5 M, 3.30 mL, 1.65 mmol) and allyl iodide (0.15 mL, 1.66 mmol) to afford **2h** as a gummy solid (0.700 g, 88%) in a de of > 99%.

$[\alpha]_D^{20}$ = –28.3º, (*c* = 1, $CHCl_3$); IR (ν_{max}/cm^{-1}) 3055, 2920, 1728, 1669, 1366, 1175; ^1H NMR (300 MHz, $CDCl_3$) δ 7.94 (d, *J* = 7.8 Hz, 1H), 7.69 (d, *J* = 8.6 Hz, 2H), 7.46 (d, *J* = 7.5 Hz, 1H), 7.40 (s, 1H), 7.30–6.94 (m, 11H), 6.81 (d, *J* = 8.6 Hz, 2H), 5.61–5.46 (m, 1H), 5.05–4.80 (m, 5H), 3.80 (s, 3H), 3.57–3.36 (m, 3H), 3.03–2.79 (m, 2H), 2.71 (s, 3H), 2.31 (s, 3H), 0.67 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.0, 168.6, 159.7, 155.2, 144.8, 136.4, 135.5, 134.9, 133.2, 131.9, 130.5, 129.9, 128.5, 128.1, 127.8, 127.1, 126.9, 126.2, 125.9, 124.6, 123.0, 119.7, 118.8, 117.9, 113.9, 113.7, 66.7, 60.5, 59.3, 55.5, 54.1, 39.5, 28.2, 21.7, 15.0; HRMS (ESI^+) *m/z*: $[M + H]^+$ Calcd for $C_{41}H_{42}N_3O_7S$ 720.2743; Found 720.2727

4-Methoxybenzyl (R)-2-benzyl-5-(benzyloxy)-2-((4S,5R)-3,4-dimethyl-2-oxo-5-phenylimidazolidine-1-carbonyl)pentanoate ***(2i)***

Prepared according to general procedure A from **1** (0.900 g, 2.27 mmol), using KHMDS (0.5 M, 4.85 mL, 2.42 mmol, 1.2 eq), 1-benzyloxy-4-iodobutane (0.987 mg, 3.40 mmol,) prepared by standard methods from 1,4-butanediol to give 4-methoxybenzyl 5-(benzyloxy)-2-((4*S*, 5*R*)-3,4-dimethyl-2-oxo-5-phenylimidazolidine-1-carbonyl)pentanoate (1.27 g, 2.23 mmol, 97%). In this case, the reaction mixture had to be warmed to 60 ºC to achieve full conversion. A portion of this (1.200 g, 2.21 mmol), was then subjected to the second alkylation using KHMDS (0.5 M, 5.20 mL, 2.60 mmol) and benzyl bromide (0.40 mL, 3.36 mmol) to afford **2i** as a gummy solid (1.250 g, 89%) in a de of 93%.

$[\alpha]_D^{20}$ = –4.2º, (*c* = 1.0, CH_3Cl); IR (ν_{max}/cm^{-1}) 3063, 2937, 1723, 1676; ^1H NMR (300 MHz, $CDCl_3$) δ 7.38–6.92 (m, 15H), 6.88–6.77 (m, 4H), 5.25 (d, *J* = 8.7 Hz, 1H), 4.96 (d, *J* = 11.7

Hz, 1H), 4.85 (d, *J* = 11.7 Hz, 1H), 4.46 (d, *J* = 12.6 Hz, 1H), 4.41 (d, *J* = 12.6 Hz, 1H), 3.79 (s, 3H), 3.71 (dq, *J* = 8.7, 6.6 Hz, 1H), 3.51–3.26 (m, 4H), 2.70 (s, 3H), 2.10–1.88 (m, 2H), 1.83-1.68 (m, 1H), 1.52-1.38 (m, 1H), 0.72 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.3, 169.8, 159.9, 155.4, 139.1, 137.0, 136.6, 130.8, 130.6, 128.4, 128.4, 128.0, 127.9, 127.9, 127.8, 127.7, 127.5, 126.5, 114.1, 73.0, 70.6, 66.5, 61.0, 60.0, 55.5, 54.4, 40.1, 30.6, 28.2, 25.1, 15.1; HRMS (ESI^+) *m/z*: $[M + H]^+$ Calcd for $C_{39}H_{43}N_2O_6$ 635.3116; Found 635.3124.

General Procedure B: synthesis of α-tertiary amines (5a-5i)

The appropriate α,α'-disubstituted auxiliary malonate (**2a-i**) (1 eq.) was dissolved in DCM (0.3 M), and anisole (1.2 eq.) was added. Trifluoroacetic acid (5-6 eq.) was introduced slowly via syringe, and the reaction mixture stirred at room temperature until the reaction was complete by TLC (2-6 h), after which solvent and excess TFA were removed on the rotary evaporator. Sat. $NaHCO_3$ was then added to pH 8 and the neutral organic material extracted three times into diethyl ether. The aqueous layer was then acidified with 1 M HCl until pH 2, extracted with EtOAc and the organic extracts combined, dried over $MgSO_4$ and concentrated under reduced pressure to afford pure carboxylic acid **3**. The acid was then dissolved in acetonitrile (0.3 M), and Et_3N (2 eq.) and diphenylphosphoryl azide (1.2 eq.) successively added. The reaction mixture was allowed to stir at rt for 3 h after which time the solvent was removed *in vacuo* and the residue filtered through a plug of silica with EtOAc/hexane (10/90) to remove excess DPPA, affording the corresponding acyl azide as a clear gum. The acyl azide was then dissolved in acetonitrile (0.3 M), which was refluxed at 85 °C. The rearrangement to isocyanate was complete within 6 hours as evidenced by TLC. The reaction mixture was cooled to 60 ºC, and HCl (6.0 M) was added to effect the hydrolysis (30 minutes). The reaction mixture was then cooled to rt and the amine isolated by extractive work-up. This involved removal of acetonitrile, addition of water and extraction once with

diethyl ether to remove non-amine material. The resultant aqueous layer was then treated with sodium hydroxide solution (5%) until pH 10-12 to liberate the amine from its hydrochloride salt and then extracted three times with ethyl acetate and once with chloroform/ethanol (75/25). The organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated to give the α-tertiary amines **4a-i**, which were pure enough by virtue of ^{1}H NMR spectroscopy for auxiliary deprotection in which the auxiliary α-tertiary amine ester (**4a-i**) was placed in anhydrous MeOH (0.1 M), and NaOMe (1.0 M, 1.1 eq.) was introduced via dropwise addition. The reaction mixture was stirred for 1 h after which time water was added and the methanol removed on a rotary evaporator. The aqueous mixture was extracted twice with ethyl acetate and once with chloroform/ethanol (75/25), and the pooled organic fractions were dried with anhydrous $MgSO_4$, filtered and concentrated. Chromatographic purification of products **5a-i** was carried out using MeOH/ DCM (5/95 to 10/90).

A full description of the sequence for **5a** is now given, but thereafter only full characterisation data will be given for final amine products **5b-i**.

*(S)-2-Benzyl-3-((4S,5R)-3,4-dimethyl-2-oxo-5-phenylimidazolidin-1-yl)-2-methyl-3-oxopropanoic acid (**3a**)*

Compound **2a** (0.820 g, 1.64 mmol) was subjected to general procedure B using anisole (0.21 mL, 1.97 mmol) and TFA (0.63 mL, 8.20 mmol) to give the corresponding acid **3a** as a colourless oil (0.592 g, 95%).

IR (ν_{max}/cm^{-1}) 2964, 1726, 1683, 1431, 1399; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (br s, 1H), 7.36–7.27 (m, 3H), 7.25–7.16 (m, 5H), 7.15–7.11 (m, 2H), 5.24 (d, J = 8.6 Hz, 1H), 3.96 (dq, J = 8.6, 6.6 Hz, 1H), 3.47 (d, J = 14.0 Hz, 1H), 3.27 (d, J = 14.0 Hz, 1H), 2.81 (s, 3H), 1.49 (s, 3H), 0.80 (d, J = 6.6 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.2, 169.5, 155.7, 136.8,

136.3, 130.5, 128.6, 128.2, 128.1, 127.0, 126.9, 60.6, 56.2, 54.5, 41.4, 28.3, 21.9, 15.0; HRMS (ESI^+) *m/z*: $[M + H]^+$ Calcd for $C_{22}H_{25}N_2O_4$ 381.1804; Found 381.1823.

3a was then committed to acyl azide formation with Et_3N (0.43 mL, 3.12 mmol), DPPA (0.40 mL, 1.87 mmol) to afford (*S*)-2-benzyl-3-((4*S*,5*R*)-3,4-dimethyl-2-oxo-5-phenylimidazolidin-1-yl)-2-methyl-3-oxopropanoyl azide:

IR (ν_{max}/cm^{-1}) 2944, 2242, 2143, 1726, 1683, 1400, 1030; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34–7.28 (m, 3H), 7.28–7.21 (m, 3H), 7.20–7.12 (m, 2H), 7.11–7.06 (m, 2H), 5.19 (d, *J* = 8.5 Hz, 1H), 3.92 (dq, *J* = 8.5, 6.6 Hz, 1H), 3.41 (d, *J* = 13.9 Hz, 1H), 3.24 (d, *J* = 13.9 Hz, 1H), 2.82 (s, 3H), 1.44 (s, 3H), 0.80 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.6, 168.8, 155.3, 136.4, 136.3, 130.4, 128.6, 128.3, 128.2, 127.1, 127.0, 60.6, 57.9, 54.4, 41.4, 28.3, 21.9, 15.0; HRMS (ESI^+) *m/z*: $[M + H]^+$ Calcd for $C_{22}H_{24}N_5O_3$ 406.1879; Found 406.1882

The azide was refluxed in toluene for 6 h followed by hydrolysis with with HCl (5 M, 2 mL) to afford α-tertiary amine (4*S*, 5*R*)-1-((S)-2-amino-2-methyl-3-phenylpropanoyl)-3,4-dimethyl-5-phenylimidazolidin2-one (**4a**) as a colourless liquid (0.449 g, 1.28 mmol, 78% from **2a**).

IR (ν_{max}/cm^{-1}) 3380, 2976, 1713, 1671, 1423, 1393, 1310; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36–7.29 (m, 3H), 7.27–7.19 (m, 5H), 7.19–7.15 (m, 2H), 5.28 (d, *J* = 8.4 Hz, 1H), 3.94 (dq, *J* = 8.4, 6.6 Hz, 1H), 3.27 (d, *J* = 13.2 Hz, 1H), 3.07 (d, *J* = 13.2 Hz, 1H), 2.86 (s, 3H), 2.37 (br s, 2H), 1.33 (s, 3H), 0.80 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.1, 156.0, 137.4, 137.0, 130.9, 128.7, 128.1, 128.1, 126.8, 126.6, 61.4, 60.6, 54.3, 44.5, 28.5, 25.6, 15.1; HRMS (ESI^+) *m/z*: $[M + H]^+$ Calcd. for $C_{21}H_{26}N_3O_2$ 352.2027; Found 352.2025.

4a (0.380 g, 1.08 mmol) was reacted with NaOMe in MeOH (1.0 M, 1.20 mL, 1.20 mmol) to afford quaternized amino acid methyl ester, methyl (*S*)-2-amino-2-methyl-3-phenylpropanoate **5a**[22] (0.159 g, 0.82 mmol, 76%) as a viscous oil in 99% ee.

$[\alpha]_D^{20} = -8.2°$, (c = 0.67, $CHCl_3$), [lit.[23] $[\alpha]_D^{20} = -14.1°$, (c = 1.6, $CHCl_3$)]; IR (ν_{max}/cm^{-1}) 3374, 3027, 2956, 1731, 1601; ^1H NMR (400 MHz, $CDCl_3$) δ 7.31–7.20 (m, 3H), 7.17–7.12 (m, 2H), 3.70 (s, 3H), 3.13 (d, J = 13.2 Hz, 1H), 2.80 (d, J = 13.2 Hz, 1H), 1.72 (br s, 2H), 1.40 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.6, 136.7, 130.1, 128.4, 127.0, 59.0, 52.2, 47.1, 26.7; HRMS (ESI^+) *m/z*: $[M + H]^+$ Calcd. for $C_{11}H_{16}NO_2$ 194.1176; Found 194.1175.

*(S)-Methyl 2-benzamido-2-methylpent-4-enoate (N-benzamide of **5b**)*

Compound **2b** (0.760 g, 1.69 mmol) was subjected to general procedure B using anisole (0.22 mL, 2.03 mmol) and TFA (0.65 mL, 8.45 mmol) to give the corresponding acid **3b** as a colourless oil (0.525 g, 94%). This was then then committed to the general modified procedure for the Curtius rearrangement with Et_3N (0.44 mL, 3.18 mmol, 2 eq), DPPA (0.41 mL, 1.91 mmol) and HCl (5 M, 3 mL) for the hydrolysis affording α-tertiary amine **4b** as a colourless liquid (0.422 g, 1.40 mmol, 83% from **2b**). **4b** (0.400 g, 1.33 mmol) was deprotected with NaOMe in MeOH (1.0 M, 1.46 mL, 1.46 mmol) to furnished the α-allyl alanine methyl ester **5b** as a light-yellow gum which was then taken up in DCM (20 mL). Anhydrous pyridine (0.12 mL, 1.52 mmol) was added followed by benzoyl chloride (0.18 mL, 1.52 mmol), and the reaction left to stir for 6 h. No work-up was performed; after removal of solvents on the rotary evaporator the residue was chromatographed directly with ethyl acetate/hexane (40/60) giving the *N*-benzamide of **5b** (0.247 g, 1.00 mmol, 75% over 2 steps) as a light-yellow gum in 89% ee.

$[\alpha]_D^{20} = +9.80°$, (c = 1.0, $CHCl_3$), [lit.[24] $[\alpha]_D^{20} = +9.74°$, (c = 1.0, $CHCl_3$)]; IR (ν_{max}/cm^{-1}) 3346, 3067, 2929, 1731, 1640; ^1H NMR (400 MHz, $CDCl_3$) δ 7.79–7.75 (m, 2H), 7.53–7.47 (m, 1H), 7.46–7.40 (m, 2H), 6.92 (s, 1H), 5.76–5.64 (m, 1H), 5.18-5.10 (m, 2H), 3.80 (s, 3H), 3.11 (ddt, J = 13.9, 7.3, 1.0 Hz, 1H), 2.67 (ddt, J = 13.9, 7.3, 1.0 Hz, 1H), 1.74 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.8, 166.6, 135.0, 132.6, 131.7, 128.7, 127.0, 119.7, 60.4, 52.9, 40.9, 23.1; HRMS (ESI^+) *m/z*: $[M + H]^+$ Calcd for $C_{14}H_{18}NO_3$ 248.1281; Found 248.1291.

*(R)-Methyl 2-amino-2-benzylpent-4-ynoate (**5c**)*

Compound **2c** (0.620 g, 1.18 mmol) was subjected to general procedure B using anisole (0.13 mL, 1.18 mmol) and TFA (0.45 mL, 5.90 mmol) to give the corresponding acid **3c** as a colourless oil (0.420 g, 1.04 mmol, 88%). This was then committed to the general modified procedure for Curtius rearrangement with Et_3N (0.29 mL, 2.08 mmol), DPPA (0.27 mL, 1.25 mmol) and HCl (5 M, 2 mL) for the hydrolysis affording yielding α-tertiary amine **4c** as a colourless liquid (0.276 g, 0.74 mmol, 62% from **2c**). Thereafter, **4c** (0.300 g, 0.800 mmol) was deprotected with NaOMe in MeOH (1.0 M, 0.88 mL, 0.88 mmol) to afford **5c** (0.158 g, 0.73 mmol, 91%) as a viscous oil in 70% ee.

IR (ν_{max}/cm^{-1}) 3380, 3281, 3029, 2950, 2320, 1738; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31–7.21 (m, 3H), 7.17–7.12 (m, 2H), 3.71 (s, 3H), 3.13 (d, *J* = 13.2 Hz, 1H), 2.87 (d, *J* = 13.2 Hz, 1H), 2.76 (dd, *J* = 16.4, 2.4 Hz, 1H), 2.51 (dd, *J* = 16.4, 2.4 Hz, 1H), 2.08 (t, *J* = 2.4 Hz, 1H), 1.82 (br s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.4, 135.9, 130.0, 128.6, 127.3, 79.6, 71.9, 61.8, 52.4, 45.3, 29.8; HRMS (ESI$^+$) *m/z*: $C_{13}H_{16}NO_2$ $[M + H]^+$ Calcd for 218.1176; Found 218.1180.

*(S)-Methyl 2-amino-2-benzylpent-4-ynoate (**5d**)*

Desilylated **2d** (0.700 g, 1.33 mmol) was subjected to general procedure B using anisole (0.15 mL, 1.33 mmol) and TFA (0.51 mL, 6.65 mmol) to give the corresponding acid **3d** as a colourless oil (0.510 g, 1.26 mmol, 95%). This was then committed to the general modified procedure for Curtius rearrangement with Et_3N (0.35 mL, 2.52 mmol), DPPA (0.33 mL, 1.51 mmol) and HCl (5 M, 2 mL) for the hydrolysis affording α-tertiary amine **4d** as a colourless liquid (0.335 g, 0.89 mmol, 67% from **2d**). **4d** (0.250 g, 0.67 mmol) was deprotected with NaOMe in MeOH (1.0 M, 0.75 mL, 0.75 mmol) to afford **5d**[25] (0.140 g, 0.65 mmol, 97%) as a viscous oil in 92% ee.

$[\alpha]_D^{20}$ = –29.0º, (*c* = 1.0, $CHCl_3$); IR (ν_{max}/cm^{-1}) 3370, 3265, 3034, 2950, 2320, 1733; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34–7.20 (m, 3H), 7.18–7.10 (m, 2H), 3.71 (s, 3H), 3.13 (d, *J* = 13.2 Hz, 1H), 2.87 (d, *J* = 13.2 Hz, 1H), 2.76 (dd, *J* = 16.4, 2.4 Hz, 1H), 2.51 (dd, *J* = 16.4, 2.4 Hz, 1H), 2.08 (t, *J* = 2.4 Hz, 1H), 1.82 (br s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.4, 135.9, 130.0, 128.6, 127.3, 79.6, 71.9, 61.8, 52.4, 45.3, 29.8; HRMS (ESI^+) *m/z*: $[M + H]^+$ Calcd for $C_{13}H_{16}NO_2$ 218.1176; Found 218.1181.

(R)-Methyl 2-amino-2-isobutylpent-4-enoate ***5e***

Compound **2e** (0.300 g, 0.61 mmol) was subjected to general procedure B using anisole (0.08 mL, 0.732 mmol) and TFA (0.23 mL, 3.05 mmol) to give the corresponding acid **3e** as a colourless oil (0.200 g, 0.54 mmol, 88%), which was then committed to Curtius rearrangement with Et_3N (0.15 mL, 1.08 mmol), DPPA (0.14 mL, 0.648 mmol) and HCl (5 M, 2 mL) for the hydrolysis affording α-tertiary amine **4e** (0.150 g, 0.44 mmol, 72% from **2e**) as a colourless liquid. **4e** (0.130 g, 0.38 mmol) was deprotected with NaOMe in MeOH (1.0 M, 0.42 mL, 0.42 mmol) to afford **5e** (0.052 g, 0.28 mmol, 74%) as an oil.

$[\alpha]_D^{20}$ = +20.8º, (*c* = 1.0, CH_2Cl_2), [lit.[26] $[\alpha]_D^{20}$ = +41.3º, (*c* = 1.0, MeOH)]; IR (ν_{max}/cm^{-1}) 3369, 2956, 1734; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.74–5.57 (m, 1H), 5.17–5.06 (m, 2H), 3.70 (s, 3H), 2.53 (dd, *J* = 13.4, 6.3 Hz, 1H), 2.15 (dd, *J* = 13.4, 8.4, 1H), 1.89–1.64 (m, 4H), 1.59–1.48 (m, 1H), 0.93 (d, *J* = 6.3 Hz, 3H), 0.82 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.9, 132.7, 119.7, 60.6, 52.1, 48.7, 45.8, 24.7, 24.4, 22.9; HRMS (ESI^+) *m/z*: $[M + H]^+$ Calcd for $C_{10}H_{20}NO_2$ 186.1494; Found 186.1496

Compound **5e** (0.020 g, 0.11 mmol) was dissolved in DCM (5 mL), and anhydrous pyridine (0.01 mL, 0.13 mmol) and benzoyl chloride (0.02 mL, 0.13 mmol) were added, and the reaction mixture was left to stir for 6 h. No work-up was performed; after removal of DCM on the rotary evaporator the residue was chromatographed directly with ethyl acetate/hexane to give the *N*-benzamide of **5e** (0.015 g, 0.052 mmol, 48%,) as a colourless gum in 99% ee.

IR (ν_{max}/cm^{-1}) 3416, 2953, 1731, 1666; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72 (m, 2H), 7.55–7.38 (m, 3H), 5.66–5.52 (m, 1H), 5.08–5.02 (m, 2H), 3.81 (s, 3H), 3.45 (dd, *J* = 13.8, 6.9 Hz, 1H), 2.70 (dd, *J* = 14.1, 5.1 Hz, 1H), 2.51 (dd, *J* = 13.8, 7.8 Hz, 1H), 1.78 (dd, *J* = 14.1, 5.1 Hz, 1H), 1.70–1.54 (m, 1H), 0.91 (d, *J* = 6.6 Hz, 3H), 0.80 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) *δ* 175.3, 166.3, 135.4, 132.4, 131.6, 128.8, 127.0, 119.2, 64.9, 52.8, 43.7, 40.5, 25.0, 24.0, 22.6; HRMS (ESI$^+$) *m/z*: $[M + H]^+$ Calcd. for $C_{17}H_{24}NO_3$ 290.1756; Found 290.1748.

(R)-Methyl 2-allyl-6-azido-2-benzamidohexanoate (N-benzamide of ***5f)***

Compound **2f** (0.850 g, 1.59 mmol) was subjected to general procedure B using anisole (0.21 mL, 1.91 mmol) and TFA (0.61 mL, 7.95 mmol) to give the corresponding acid **3f** as a colourless oil (0.570 g, 1.38 mmol, 87%). All of the acid was then committed to the general modified procedure for Curtius rearrangement with Et_3N (0.38 mL, 2.76 mmol), DPPA (0.36 mL, 1.66 mmol) and HCl (5 M, 3 mL) for the hydrolysis affording α-tertiary amine **4f** as a colourless liquid (0.437 g, 1.14 mmol, 72% from **2f**). **4f** (0.400 g, 1.04 mmol) was deprotected with NaOMe in MeOH (1.0 M, 1.2 mL, 1.20 mmol) to afford **5f** (0.185 g, 0.82 mmol, 79%) as a gummy solid, which was taken up in DCM (10 mL), anhydrous pyridine (0.17 mL, 2.06 mmol) and benzoyl chloride (0.14 mL, 1.25 mmol) added, and the reaction mixture was left to stir for 6 h at rt. The DCM was then removed on the rotary evaporator and the residue chromatographed directly with EtOAc/hexane (40/60) to give the *N*-benzamide of **5f** (0.239 g, 0.72 mmol, 89% from **5f**) as a light-yellow gum in 98% ee.

$[\alpha]_D^{20}$ = −15.8º, (*c* = 1.0, $CHCl_3$); IR (ν_{max}/cm^{-1}) 3329, 3071, 2945, 2090, 1728, 1654; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83–7.75 (m, 2H), 7.55–7.39 (m, 3H), 7.15 (br s, 1H), 5.70–5.53 (m, 1H), 5.14–5.01 (m, 2H), 3.83 (s, 3H), 3.39 (m, 1H), 3.32–3.14 (m, 2H), 2.70 (m, 1H) 2.57 (m, 1H), 1.90 (m, 1H), 1.66–1.49 (m, 2H), 1.48–1.29 (m, 1H), 1.22–1.04 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.4, 166.5, 135.1, 132.3, 131.7, 128.8, 127.0, 119.3, 65.3, 53.1,

51.2, 39.7, 34.5, 28.7, 21.7; HRMS (ESI^+) *m/z*: $[M + H]^+$ Calcd for $C_{17}H_{23}N_4O_3$ 331.1770 Found 331.1771.

(R)-Methyl 2-allyl-2-benzamido-6-((tert-butoxycarbonyl)amino)hexanoate (N^2-Bz, N^6-Boc α-allyllysine methyl ester)

The *N*-benzamide of **5f** (0.065 g, 0.197 mmol) and PPh_3 (0.103 g, 0.393 mmol) were dissolved in THF/H_2O (6/1, 5 mL) and stirred at rt for 9 h to convert the azide to the primary amine. This was followed by the addition of Boc_2O (0.086 g, 0.393 mmol) in THF (5 mL) in which *N*-protection was complete within 15 minutes as indicated by tlc. Thereafter, THF was removed on the rotary evaporator, water (5 mL) was added and the solution extracted with EtOAc (3 x 10 mL). The combined organic fractions were dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford a residue that was chromatographed using EtOAc/hexane (15/85) delivering N^2-Bz, N^6-Boc α-allyllysine methyl ester as a thick, light-yellow oil (0.060 g, 0.149 mmol, 76% over two steps) in 98% ee.

$[\alpha]_D^{20} = -12.8^o$, (*c* = 1.0, $CHCl_3$); IR (ν_{max}/cm^{-1}) 3407, 3339, 3071, 2929, 1733, 1686, 1654; ^1H NMR (300 MHz, $CDCl_3$) δ 7.83–7.73 (m, 2H), 7.55–7.37 (m, 3H), 7.14 (s, 1H), 5.69–5.52 (m, 1H), 5.10–4.95 (m, 2H), 4.55 (br s, 1H), 3.81 (s, 3H), 3.34 (dd, *J* = 13.9, 7.3 Hz, 1H), 3.12–2.98 (m, 2H), 2.73–2.61 (m, 1H), 2.57 (dd, *J* = 13.9, 7.3 Hz, 1H), 1.95–1.80 (m, 1H), 1.52–1.30 (m, 3H), 1.39 (s, 9H), 1.14–0.94 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.4, 166.4, 156.1, 135.1, 132.4, 131.6, 128.7, 127.0, 119.2, 79.2, 65.2, 53.0, 40.2, 39.7, 34.6, 29.8, 28.5, 21.5; HRMS (ESI^+) *m/z*: $[M + H]^+$ Calcd. for $C_{22}H_{33}N_2O_5$ 405.2380; Found 405.2389.

*(S)-Methyl 2-amino-3-(4-bromophenyl)-2-methylpropanoate (**5g**)*

Compound **2g** (0.800 g, 1.38 mmol) was subjected to general procedure B using anisole (0.15 mL, 1.38 mmol) and TFA (0.53 mL, 6.91 mmol) to give the corresponding acid **3g** as a colourless oil (0.500 g, 79%). This was then committed to the general modified procedure for

Curtius rearrangement with Et_3N (0.30 mL, 2.18 mmol), DPPA (0.28 mL, 1.31 mmol) and HCl (5 M, 2 mL) for the hydrolysis affording α-tertiary amine **4g** as a colourless liquid (0.411 g, 0.96 mmol, 69% from **2g**). **4g** (0.400 g, 0.93 mmol) was deprotected with NaOMe and MeOH (1.0 M, 1.0 mL, 1.00 mmol) to give **5g** (0.180 g, 0.66 mmol, 71%) as a viscous oil in 98% ee.

$[\alpha]_D^{20}$ = –12.0º, (*c* = 1.0, CH_2Cl_2), [lit.[27] $[\alpha]_D^{20}$ = +17.4º for the (*R*)-isomer, (*c* = 1.0, $CHCl_3$)]; IR (ν_{max}/cm^{-1}) 3384, 2938, 1725; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 (d, *J* = 8.3 Hz, 2H), 7.00 (d, *J* = 8.3 Hz, 2H), 3.67 (s, 3H), 3.04 (d, *J* = 13.2 Hz, 1H), 2.73 (d, *J* = 13.2 Hz, 1H), 1.72 (br s, 2H), 1.35 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) *δ* 177.2, 135.6, 131.8, 131.5, 121.1, 58.8, 52.2, 46.3, 26.5; HRMS (ESI$^+$) *m/z*: $[M + H]^+$ Calcd. for $C_{11}H_{15}{}^{79}BrNO_2$ 272.0281; Found 272.0294.

*Methyl (S)-2-amino-2-((1-tosyl-1H-indol-3-yl)methyl)pent-4-enoate (**5h**)*

Compound **2h** (0.500 g, 0.70 mmol) was subjected to general procedure B using anisole (0.09 mL, 0.83 mmol) and TFA (0.53 mL, 6.9 mmol, 10 eq) to give acid **3h** as a colourless oil after column chromatography (0.300 g, 0.50 mmol, 72%) This was then committed to the general modified procedure for Curtius rearrangement with Et_3N (0.14 mL, 1.00 mmol), DPPA (0.13 mL, 0.60 mmol). The acyl azide formed was dissolved in *p*-xylene and heated at 125 ºC for 6 h followed by HCl (1.0 M, 4 mL) for the hydrolysis affording α-tertiary amine **4h** as a colourless liquid (0.251 g, 0.44 mmol, 63% from **2h**). **4h** (0.050 g, 0.088 mmol) was deprotected with NaOMe in MeOH (0.1 mL, 0.1 mmol, 1.0 M) to give **5h** (0.027 g, 0.066 mmol, 75%) as a colourless oil in > 99% ee.

$[\alpha]_D^{20}$ = +9.9º, (*c* = 1, $CHCl_3$); IR (ν_{max}/cm^{-1}) 3375, 2968, 1730, 1367; ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 7.95 (d, *J* = 7.2 Hz, 1H), 7.71 (d, *J* = 8.4 Hz, 2H), 7.54 (d, *J* = 7.5 Hz, 1H), 7.39 (s, 1H), 7.33–7.17 (m, 4H), 5.78–5.64 (m, 1H), 5.21–5.14 (m, 2H), 3.60 (s, 3H), 3.20 (d, *J* = 14.1 Hz, 1H), 2.91 (d, *J* = 14.1 Hz, 1H), 2.71 (dd, *J* = 13.5, 6.6 Hz, 1H), 2.38–2.25 (m, 1H),

2.33 (s, 3H), 1.61 (br s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.6, 145.0, 135.4, 135.2, 132.5, 131.5, 130.0, 126.9, 125.1, 124.9, 123.3, 120.1, 120.0, 117.7, 113.8, 62.1, 52.3, 44.5, 35.2, 21.7; HRMS (ESI$^+$) *m/z*: $[M + H]^+$ Calcd for $C_{22}H_{25}N_2O_4S$ 413.1535; Found 413.1528**.**

*(R)-Methyl 2-benzyl-5-(benzyloxy)-2-((tert-butoxycarbonyl)amino)pentanoate (N-Boc derivative of **5i**)*

Compound **2i** (1.20 g, 1.89 mmol) was subjected to general procedure B using anisole (0.25 mL, 2.27 mmol) and TFA (0.72 mL, 9.46 mmol) to give acid **3i** as a colourless oil (0.900 g, 1.75 mmol, 92%). This was then committed to the general modified procedure for Curtius rearrangement with Et_3N (0.48 mL, 3.41 mmol), DPPA (0.44 mL, 2.05 mmol) and HCl (5 M, 3 mL) for the hydrolysis affording α-tertiary amine **4i** as a colourless liquid (0.725 g, 1.49 mmol, 79% from **2i**). **4i** (0.370 g, 0.76 mmol) was deprotected with NaOMe in MeOH (1.0 M, 0.84 mL, 0.84 mmol) to afford **5i** (0.170 g, 0.52 mmol, 68%) as a clear gum, which was reacted with Boc_2O (0.170 g, 0.78 mmol) in *t*-BuOH (10 mL) overnight at rt. Following removal of *t*-BuOH on the rotary evaporator, the residue was chromatographed directly using EtOAc/hexanes (10/90) to give the *N*-Boc derivative of **5i** (0.169 g, 0.39 mmol, 76% from **5i**) as a gummy solid in 90% ee.

$[\alpha]_D^{20}$ = –42.5º, (*c* = 1.0, $CHCl_3$); IR (ν_{max}/cm^{-1}) 3332, 2955, 2919, 1733, 1670; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39–7.18 (m, 8H), 7.09–7.01 (m, 2H), 5.38 (br s, 1H), 4.49 (s, 2H), 3.74 (s, 3H), 3.60 (d, *J* = 13.5 Hz, 1H), 3.53–3.41 (m, 2H), 3.11 (d, *J* = 13.5 Hz, 1H), 2.58–2.36 (m, 1H), 2.08–1.90 (m, 1H), 1.76–1.57 (m, 1H), 1.48 (s, 9H), 1.52–1.31 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.6, 154.2, 138.7, 136.7, 130.0, 128.5, 128.3, 127.7, 127.6, 126.9, 79.3, 72.9, 70.0, 65.0, 52.6, 41.2, 32.5, 28.6, 24.8; HRMS (ESI$^+$) *m/z*: $[M + H]^+$ Calcd for $C_{25}H_{34}NO_5$ 428.2431; Found 428.2440.

(R)-a-Benzylproline Methyl ester **6**

N-Boc **5i** (0.150 g, 0.35 mmol) was dissolved in deoxygenated MeOH (10 mL), and Pd/C (10 wt %, 0.040 g, 0.035 mmol) was carefully added under nitrogen gas flow. The reaction was then placed under a hydrogen atmosphere and stirred at rt for 2 h, following which it was filtered through Celite®, concentrated and committed to column chromatography directly using EtOAc/hexanes (20/80) to yield the corresponding alcohol (0.101 g, 0.30 mmol, 85%) as a viscous oil. The latter (0.060 g, 0.18 mmol) was dissolved in DCM (3 mL) and to this was then added pyridine (0.30 mL, 0.35 mmol), DMAP (0.011 g, 0.03 mmol) and mesyl chloride (0.030 mL, 0.35 mmol) and the reaction stirred at rt for 4 h. The mixture was transferred to a separating funnel and washed with aqueous saturated sodium bicarbonate (15 mL) and the aqueous layer extracted with DCM (3 x 20 mL). Pooled organic fractions were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* and the residue was committed to flash chromatography using EtOAc/hexanes (10/90) to yield the mesylate (0.070 g, 0.17 mmol, 92% from the alcohol) as a colourless gum.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28–7.18 (m, 3H, aromatic), 7.07–6.98 (m, 2H, aromatic), 5.38 (broad s, 1H), 4.28–4.15 (m, 2H), 3.77 (s, 3H), 3.60 (d, J = 13.5 Hz, 1H), 3.06 (d, J = 13.5 Hz, 1H), 3.01 (s, 3H), 2.66–2.52 (m, 1H), 2.10–1.98 (m, 1H), 1.85–1.71 (m, 1H), 1.65–1.52 (m, 1H), 1.41 (s, 9H).

To the mesylate (0.070 g, 0.17 mmol) dissolved in DCM (2 mL) and cooled to 0 ºC was added TFA (0.07 mL, 0.92 mmol). Stirring was continued at this temperature for 2 h, after which time TLC analysis indicated complete deprotection of the starting material. The intermediate free amine was not isolated and the reaction mixture was concentrated *in vacuo* to remove solvent and TFA. The yellowish liquid was re-taken up in THF (3 mL) and triethylamine (0.27 mL, 1.93 mmol) was added. The solution was stirred at rt for 1h, after which, following THF removal on the rotary evaporator, water (15 mL) was added and the

aqueous layer was extracted with EtOAc (3 x 30 mL). The combined organic fractions were dried over anhydrous $MgSO_4$, filtered, concentrated and the resultant residue was chromatographed using EtOAc/hexanes to furnish (*R*)-α-benzylproline methyl ester[28] **6** (0.032 g, 0.15 mmol, 86%) as a clear viscous liquid in 91% ee.

$[\alpha]_D^{20} = -10.0°$, (*c* = 1.0, $CHCl_3$); IR (ν_{max}/cm^{-1}) 3349, 3029, 2950, 1733; ^1H NMR (300 MHz, $CDCl_3$) δ 7.32–7.11 (m, 5H), 3.66 (s, 3H), 3.17 (d, *J* = 13.1 Hz, 1H), 3.04–2.92 (m, 2H), 2.87 (d, *J* = 13.1 Hz, 1H), 2.29–2.19 (m, 1H), 2.15 (br s, 1H) 1.91–1.63 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.0, 137.6, 129.8, 128.3, 126.8, 70.7, 52.1, 46.1, 45.5, 35.8, 24.5; HRMS (ESI^+) *m/z*: $[M + H]^+$ Calcd $C_{13}H_{18}NO_2$ 220.1332; Found 220.1338.

SUPPORTING INFORMATION

^1H and ^{13}C NMR spectra and HPLC traces of all compounds are presented. This material is available free of charge via the Internet at http://pubs.acs.org.

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