PERKIN 1

A new route to hydrophobic amino acids using copper-promoted reactions of serine-derived organozinc reagents

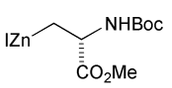
Hervé J. C. Deboves,[a] Urszula Grabowska,[b] Adriana Rizzo[b] and Richard F. W. Jackson *[a]

[a] *Department of Chemistry, Bedson Building, The University of Newcastle, Newcastle upon Tyne, UK NE1 7RU*
[b] *Medivir UK Ltd, Peterhouse Technology Park, 100 Fulbourn Road, Cambridge, UK CB1 9PT*

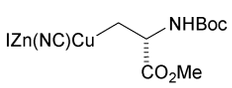
Received (in Cambridge, UK) 30th August 2000, Accepted 4th October 2000
First published as an Advance Article on the web 1st December 2000

Copper-catalysed reaction of the serine-derived zinc reagent **1** with allylic electrophiles gives products arising formally from both S_N2 and S_N2' pathways. These constitutional isomers can be separated, either directly, or in the case of (2*S*)-2-*tert*-butoxycarbonylamino-6-methylhept-5-enoic acid methyl ester (**11**) and (2*S*)-2-*tert*-butoxycarbonylamino-4,4-dimethylhex-5-enoic acid methyl ester (**12**) by selective epoxidation of **11**. Hydrogenation of the double bond, followed by protecting group manipulation, allows the synthesis of the Fmoc-protected amino acids **3**–**7** ready for automated peptide synthesis.

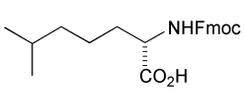
The synthesis of unnatural analogues of proteinogenic amino acids is an important goal in the context of understanding receptor binding.[1] We have developed effective methods for the conversion of readily available enantiomerically pure natural amino acids (serine, aspartic acid, glutamic acid) into unnatural amino acids using organometallic chemistry without loss of stereochemical integrity.[2–5] We have established that the zinc–copper reagent **2**, prepared from the zinc reagent **1**, reacts with allylic and propargylic (prop-2-ynyl) electrophiles to give enantiomerically pure unsaturated amino acids in moderate to good yields.[3] It was therefore of interest to establish whether this approach might also be amenable to the synthesis of a range of homologues of valine, leucine and isoleucine, in which the side chains contain a series of methyl branches. The Fmoc-protected amino acids **3**–**7** were therefore identified as targets, and we have explored a route to these compounds using the copper-promoted reaction of the zinc reagent **1** with a range of highly substituted allylic electrophiles. The unprotected analogue of **3** had previously been isolated by hydrolysis of the peptide antibiotic Longicatenamycin,[6,7] along with the lower and higher homologues.



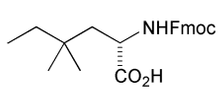
1



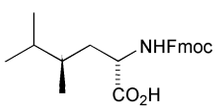
2



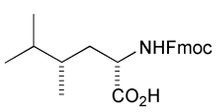
3



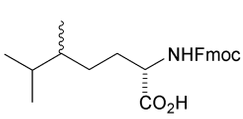
4



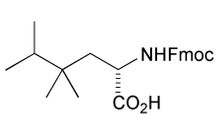
5a



5b



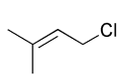
6



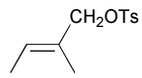
7

Results and discussion

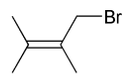
In our original work,[3] we had employed the stoichiometric transmetallation of the zinc reagent **1** to the zinc–copper reagent **2** using CuCN·2LiCl, prior to addition of the electrophile. While this process is reliable, the need to exercise appropriate precautions during the reaction due to the toxicity of cyanide, and especially during the work-up, is a significant drawback. This prompted us to explore the use of catalytic amounts of copper, most specifically CuBr·DMS, which has recently been reported to catalyse the reaction between β-amino zinc reagents and both propargyl and allenyl halides.[8,9] In addition, we were concerned that the electrophiles that we proposed to use, **8**–**10**, might be susceptible to copper-catalysed isomerisation in the presence of halide ion, which in turn would lead to mixtures of products provided the usual S_N2' pathway was followed in the substitution. The use of catalytic amounts of copper might be expected to minimise this problem.



8



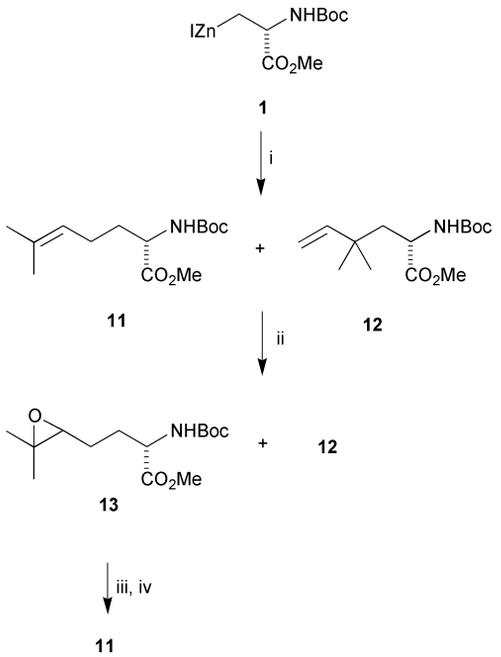
9



10

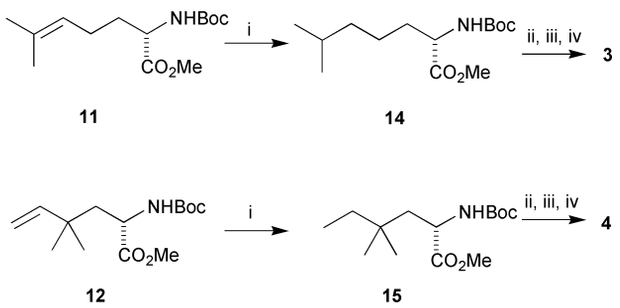
Reaction of the zinc–copper reagent, prepared under our previously described conditions, with 3,3-dimethylallyl chloride gave a mixture of the constitutional isomers **11** and **12**, in a 58 : 42 ratio (93%). When the zinc reagent **1** was treated with 3,3-dimethylallyl chloride in the presence of a catalytic amount of CuBr·DMS, the two isomers **11** and **12** were isolated in excellent overall yield (90%), and in a ratio of 55 : 45. These results suggest that while the work-up can be much simplified by the use of catalytic amounts of copper, the regiochemical outcome of the reaction is not altered. Unfortunately, it did not prove possible to separate **11** and **12**, so we took advantage of the very well-established higher reactivity of trisubstituted alkenes, compared with terminal alkenes, towards MCPBA.[10] Thus, treatment of the mixture of **11** and **12** with MCPBA resulted in selective epoxidation of **11** to give **13** (as a mixture of diastereoisomers), leaving **12** untouched. The separation of alkene **12** from epoxide **13** proved straightforward, and epoxide **13** was converted back into the terminal alkene **11** by treatment with the reagent derived from WCl_6 and BuLi (Scheme 1).[11,12]

 DOI: 10.1039/b007032g



Scheme 1 *Reagents and conditions*: i CuBr·DMS, $(CH_3)_2C{=}CHCH_2Cl$; ii MCPBA, $CHCl_3$, room temp., 2 h; iii separation; iv WCl_6–BuLi, −78 °C, then 0–5 °C, 30 min, room temp., 1 h.

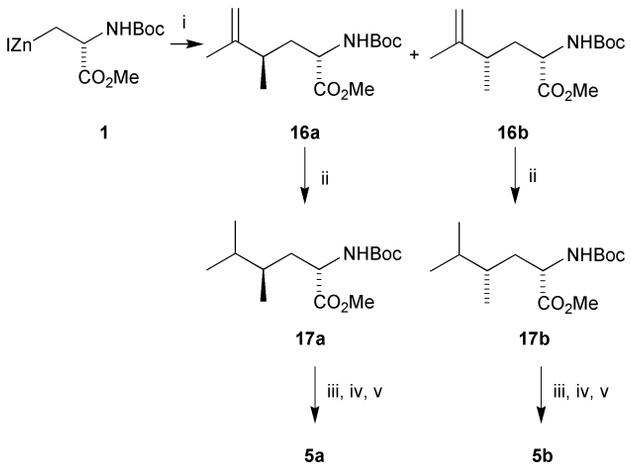
Separate hydrogenation of compounds **11** and **12** proceeded smoothly to give the saturated analogues **14** and **15**. These two compounds were fully characterised, and then converted into the Fmoc-protected amino acids **3** and **4** by a series of standard protecting group manipulations (Scheme 2).



Scheme 2 *Reagents and conditions*: i H_2, Pd/C, EtOH, room temp.; ii LiOH, THF–H_2O, 1:1, room temp.; iii HCl (4 M), dioxane; iv FmocCl, Na_2CO_3, H_2O, dioxane, room temp.

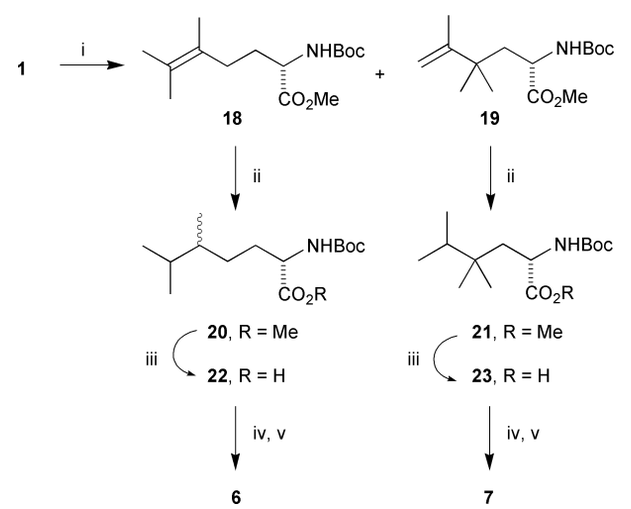
In order to prepare the two diastereoisomers **5a** and **5b**, it was necessary to treat the zinc reagent **1** with the tosylate **9**, which was prepared in two steps from 2-methylbut-2-enoic acid.[13,14] Tosylate **9**, as reported in the literature,[14] is very unstable, and it is necessary to store the compound in solution. Nevertheless, the CuBr·DMS catalysed reaction gave the separable diastereoisomers **16a** (32%) and **16b** (19%) in moderate combined yield. The relative stereochemistry of the racemic *N*-acetyl analogues of **16a** and **16b**, prepared by a Lewis acid catalysed ene reaction between methyl 2-acetamidoacrylate and 2-methylbut-2-ene, had been tentatively assigned by analogy with the outcome of a related reaction.[15] We have therefore converted compound **16b** into the corresponding *N*-acetyl derivative, which exhibited identical ^{13}C NMR data to that reported in the literature.[15] Compounds **16a** and **16b** were then separately converted in an analogous series of steps to those already described, *via* the characterised saturated analogues **17a** and **17b**, into the target Fmoc-protected acids **5a** and **5b** (Scheme 3).

With the aim of preparing the homologues of compounds **5a** and **5b**, the copper-catalysed reaction of the zinc reagent **1**



Scheme 3 *Reagents and conditions*: i CuBr·DMS, (*E*)-$CH_3CH{=}C(CH_3)CH_2OTs$; ii H_2, Pd/C, EtOH, room temp.; iii LiOH, THF–H_2O, 1:1, room, temp.; iv HCl (4 M), dioxane; v FmocCl, Na_2CO_3, H_2O, dioxane, room temp.

with the bromide **10**, prepared by HBr addition to 2,3-dimethylbutadiene,[16] was investigated. The two constitutional isomers **18** (29%) and **19** (30%) were isolated, and these could be separated by flash chromatography. This reaction was carried out on a 30 mmol scale, and demonstrates the capability of this method to prepare gramme amounts of material. The unsaturated amino acids **18** and **19** were then converted *via* the saturated analogues **20** (isolated as an inseparable mixture of diastereoisomers) and **21**, and the derived Boc-protected amino acids **22** and **23** into the targets **6** (also isolated as an inseparable mixture of diastereoisomers) and **7**, respectively (Scheme 4).



Scheme 4 *Reagents and conditions*: i CuBr·DMS, $(CH_3)_2C{=}C(CH_3)CH_2Br$; ii H_2, Pd/C, EtOH, room temp.; iii LiOH, THF–H_2O, 1:1, room, temp.; iv HCl (4 M), dioxane; v FmocCl, Na_2CO_3, H_2O, dioxane, room temp.

Conclusions

It appears that the normal course of substitution reactions of allylic electrophiles with zinc–copper reagents, in which the products from the S_N2' pathway predominate, is no longer followed when highly substituted electrophiles are used. Electrophiles in which the S_N2' pathway would require attack at a fully substituted position, as is the case for **8** and **10**, tend to give significant amounts of the products formally derived by the S_N2 pathway. At this stage, we cannot rule out the possibility that the products formally derived by the S_N2 pathway actually arise by an initial isomerisation of the electrophile

(which is known to be promoted by copper salts, even if these are present only in sub-stoichiometric amounts), rather than an S_N2 pathway.

From a preparative point of view, we have shown how the copper-catalysed reaction of the serine-derived zinc reagent **1** with substituted allylic electrophiles can be used to good effect in the preparation of a series of amino acids with branched hydrophobic side-chains. Although constitutional isomers are formed, these can be separated.

Experimental

Dry DMF was distilled from calcium hydride and stored over 4 Å molecular sieves. Dry dichloromethane was distilled from calcium hydride. Dry THF was distilled from potassium benzophenone ketyl. Petroleum ether refers to the fraction with a boiling point between 40–60 °C. Specific rotations were measured on a PolAAr 2000 instrument at the stated temperature and are given in units of 10^{-1} deg cm^2 g^{-1}. IR spectra were recorded on a Nicolet 20PCIR spectrometer at the University of Newcastle as thin films. Mass spectra (*m*/*z*) (Electrospray) were obtained using a Fisons/VG analytical system at Medivir UK, Cambridge or measured on a Micromass Autospec M spectrometer in electron impact (EI) mode at the University of Newcastle. HRMS mass spectra (*m*/*z*) (Electrospray) were recorded using a Q-TOF Micromass spectrometer by University of Cambridge Spectrometry Service or a Micromass Autospec M spectrometer in EI mode at the University of Newcastle. Nuclear magnetic resonance (NMR) spectra were recorded at the field strength in the solvents indicated, using standard pulse sequences on a DRX-500 machine by the University of Cambridge NMR Department or on a Bruker AC 200 (200 MHz) or JEOL LA 500 (500 MHz) instrument at the University of Newcastle. Chemical shifts are expressed in parts per million (δ) and are referenced to residual signals of the solvent. Coupling constants (*J*) are expressed in Hz. Elemental analyses were carried out either by University of Cambridge Microanalysis Service or by University of Newcastle Microanalysis Service. Unless otherwise specified, all solvents and reagents were obtained from commercial suppliers and used without further purification. HPLC samples were run on a Vydac Phenomenex Jupiter C_4 (5μ) 250 × 4.6 mm analytical column using an automated Gilson 215/233XL. A gradient of 10–90% B in A, 2–30 min, 1.5 cm^3 min^{-1}, where solvent A = 0.1% aq. TFA and solvent B = acetonitrile–10% A, with UV detection at 215 nm. Thin layer chromatography (TLC) was performed on precoated plates (Merck aluminium sheets silica 60 F254, Art. no. 5554). Visualisation of compounds was achieved by illumination under ultraviolet light (254 nm) or using an appropriate staining reagent. Flash column chromatography was performed on silica gel 60 (Merck 9385).

General procedure for the zinc coupling reactions

Zinc dust (150 mg, 2.29 mmol, 3.0 eq., Aldrich) was weighed into a 25 cm^3 round bottom flask with a side arm and fitted with a three way tap. The zinc powder was heated with a heat gun under vacuum and the flask was flushed with nitrogen and evacuated and flushed a further three times. With the flask filled with nitrogen, dry DMF (0.5 cm^3) was added. Trimethylsilyl chloride (0.029 cm^3, 0.23 mmol, 0.3 eq.) was added and the zinc slurry was vigorously stirred for a further 30 min. *N*-(*tert*-Butoxycarbonyl)-3-iodo-L-alanine methyl ester[3] (247 mg, 0.75 mmol, 1.0 eq.) dissolved in dry DMF (0.5 cm^3) was added dropwise, *via* syringe, to the activated zinc slurry at 0 °C prepared as described above. The reaction mixture was then allowed to warm up to room temperature and stirred for 1 h to give the organozinc reagent. Whilst the zinc insertion reaction was in progress, CuBr·DMS (21 mg, 0.10 mmol, 0.13 eq.) was weighed into a 25 cm^3 round bottom flask fitted with a three way tap and dried gently with a heat gun under vacuum until CuBr·DMS changed appearance from a brown powder to a light green powder. Dry DMF (0.5 cm^3) was then added followed by addition of the electrophile (1-chloro-2-methylbut-2-ene, toluene-4-sulfonic acid (*E*)-2-methylbut-2-enyl ester or 1-bromo-2,3-dimethylbut-2-ene) (1.00 mmol, 1.3 eq.). The reaction mixture was then cooled to −15 °C. Stirring of the organozinc reagent solution was stopped to allow the zinc powder to settle and the supernatant was carefully removed *via* syringe (care taken to avoid transferring too much zinc powder) and added dropwise to the solution of electrophile and copper catalyst. The cooling bath was removed and the solution was stirred at room temperature overnight. Ethyl acetate (20 cm^3) was added and stirring was continued for a further 15 min. The reaction mixture was transferred to a separating funnel and a further aliquot of EtOAc (30 cm^3) was added. The organic phase was washed successively with 1 M $Na_2S_2O_3$ (20 cm^3), water (2 × 20 cm^3), brine (40 cm^3), dried (Na_2SO_4 or $MgSO_4$) and filtered. The solvent was removed *in vacuo* and the crude product purified by flash chromatography on silica gel as described.

Additional general procedures

Hydrogenation of alkenes. The alkene (1.00 mmol) was dissolved in ethanol (10 cm^3), 10% palladium on carbon (80 mg) added and hydrogen introduced. Once the reaction was judged to have reached completion (TLC, HPLC or MS), the hydrogen was removed, the reaction filtered through Celite and the catalyst washed with ethanol (30 cm^3). The combined organic filtrate was concentrated *in vacuo* and the alkane used directly in the subsequent reaction or purified by flash chromatography on silica gel as described.

Saponification of methyl esters. The methyl ester (1.00 mmol) was dissolved in THF (6 cm^3) and whilst stirring, a solution of LiOH (1.20 mmol, 1.2 eq.) in water (6 cm^3) was added dropwise. Once the reaction was judged to have reached completion (TLC, HPLC or MS), the THF was removed *in vacuo* and diethyl ether (10 cm^3) added to the residue. The reaction mixture was acidified with 1.0 M HCl until pH 3. The organic phase was then removed and the aqueous layer extracted with diethyl ether (2 × 10 cm^3). The combined organic extracts were dried over magnesium sulfate, filtered and the solvent removed *in vacuo* to give the carboxylic acid used directly in the subsequent reaction or purified by flash chromatography on silica gel as described.

Removal of *N*-Boc protecting group. The *N*-Boc protected material (1.00 mmol) was cooled to 0 °C and 4 M HCl in dioxane (5 cm^3) was added dropwise. When the reaction was judged to have reached completion (TLC, HPLC or MS), the solvents were removed *in vacuo* to yield the amine hydrochloride which was used directly in the subsequent reaction.

Fmoc protection of amines. The amine hydrochloride (1.00 mmol) in 1,4-dioxane (2 cm^3) was cooled to 0 °C and 10% sodium carbonate (2.20 mmol, 2.2 eq., 4 cm^3) added. The biphasic reaction mixture was stirred vigorously and Fmoc–Cl (1.10 mmol, 1.1 eq.) in dioxane (2 cm^3) was added over 1 h. Once the reaction was judged to have reached completion (TLC, HPLC or MS), diethyl ether (10 cm^3) was added and the reaction mixture acidified to pH 3 with 1 M HCl. The organic phase was removed and the aqueous layer extracted with diethyl ether (2 × 10 cm^3). The combined organic extracts were dried over sodium sulfate, filtered, the solvent removed *in vacuo* and the residue purified by flash chromatography using silica gel.

(2*S*)-2-*tert*-Butoxycarbonylamino-4,4-dimethylhex-5-enoic acid methyl ester 12, (2*S*)-2-*tert*-butoxycarbonylamino-4-[(2*S*)-3,3-dimethyloxiranyl]butyric acid methyl ester 13a and (2*S*)-2-*tert*-butoxycarbonylamino-4-[(2*R*)-3,3-dimethyloxiranyl]butyric acid methyl ester 13b

Following the general procedure for zinc coupling reactions, 1-chloro-3-methylbut-2-ene (0.110 cm^3, 0.98 mmol) was coupled to *N*-(*tert*-butoxycarbonyl)-3-iodo-L-alanine methyl ester (247 mg, 0.75 mmol) in the presence of CuBr·DMS (21 mg, 0.10 mmol) to give a residue which was purified by flash column chromatography over silica gel eluting with EtOAc–heptane (1:9, v/v). Fractions were pooled and reduced *in vacuo* to give on the basis of ^{1}H NMR spectroscopy a mixture of regioisomers (183 mg, 90%) (45:55 formal S_N2' *vs.* S_N2), inseparable by column chromatography, as a colourless oil.

To a mixture of isomers **11** and **12** (190 mg, 0.70 mmol) in chloroform (3 cm^3) was added dropwise over 5 min, 3-chloroperbenzoic acid (164 mg, 85% pure, 0.81 mmol, 1.15 eq.) in chloroform (2 cm^3). The reaction mixture was stirred at room temperature for a further 2 h. The reaction mixture was then washed successively with 1 M $Na_2S_2O_5$ (5 cm^3), saturated sodium bicarbonate solution (5 cm^3) and brine (10 cm^3). The organic phase was dried over sodium sulfate, filtered, the solvent removed *in vacuo* and the residue was purified by flash chromatography over silica gel eluting with EtOAc–heptane (1:9, v/v). Three products were obtained; (2*S*)-2-*tert*-butoxycarbonylamino-4,4-dimethylhex-5-enoic acid methyl ester **12** was eluted first and further elution afforded an inseparable mixture of (2*S*)-2-*tert*-butoxycarbonylamino-4-[(2*S*)-3,3-dimethyloxiranyl]butyric acid methyl ester **13a** and (2*S*)-2-*tert*-butoxycarbonylamino-4-[(2*R*)-3,3-dimethyloxiranyl]butyric acid methyl ester **13b**. Fractions containing the initial component were pooled and reduced *in vacuo* to give (2*S*)-2-*tert*-butoxycarbonylamino-4,4-dimethylhex-5-enoic acid methyl ester **12** (93 mg, 49%) as a colourless oil. Analytical HPLC t_r = 21.45 min (95%); $[\alpha]_D^{18}$ +18.7 (*c* 0.32 in CH_2Cl_2); ν_{max}(film)/cm^{-1} 3369 (s), 3084 (m), 2965 (s), 1748 (s), 1715 (s), 1517 (s), 1167 (s), 1007 (s) and 914 (s); δ_H (500 MHz; $CDCl_3$) 1.06 (6H, s, CH_2=CHC(CH_3)$_2$), 1.42 (9H, s, C(CH_3)$_3$), 1.55 (1H, dd, *J* 14 and 9, NHCHCH_{2A}), 1.82 (1H, dd, *J* 14 and 4, NHCHCH_{2B}), 3.69 (3H, s, CO_2CH_3), 4.30 (1H, br m, NHC*H*CO_2CH_3), 4.83 (1H, br d, *J* 7, NH), 4.97 (2H, m, CH_2=CH) and 5.78 (1H, dd, J_{trans} 17.5 and J_{cis} 11, CH_2=C*H*); δ_C (125 MHz; $CDCl_3$) 26.93 (CH_2=CHC(*C*H_3)$_2$), 28.34 (C(*C*H_3)$_3$), 36.33 (CH_2=CH*C*-(CH_3)$_2$), 45.06 (NHCH*C*H_2), 51.25 (NH*C*HCO_2CH_3), 52.15 (CO_2*C*H_3), 79.77 (*C*(CH_3)$_3$), 111.39 (*C*H_2=CH), 146.87 (CH_2=*C*H), 154.97 (OC(O)NH) and 174.04 (NHCH*C*O_2CH_3); HRMS 215.1152 ($M^+ - C_4H_8$, $C_{10}H_{17}NO_4$ requires 215.1158 (δ 2.8 ppm)); *m*/*z* (Electrospray-MS) 272 (40%) and 216 (100%).

Pooling together the fractions containing later-eluting components gave a mixture of (2*S*)-2-*tert*-butoxycarbonylamino-4-[(2*S*)-3,3-dimethyloxiranyl]butyric acid methyl ester **13a** and (2*S*)-2-*tert*-butoxycarbonylamino-4-[(2*R*)-3,3-dimethyloxiranyl]butyric acid methyl ester **13b** (55 mg, 27%) as a colourless oil. (^{1}H NMR spectroscopy showed a mixture of diastereoisomers had been obtained in a 3.5:1 ratio. No attempt was made to establish which isomer was formed preferentially.) $[\alpha]_D^{23}$ +12.0 (*c* 1.02 in CH_2Cl_2); ν_{max}(film)/cm^{-1} 2976 (br), 2931 (s), 1747 (s), 1716 (s), 1391 (s) and 1367 (s); δ_H (500 MHz; $CDCl_3$) 1.26 (3H, s, (CH_3)$_{2A}$), 1.31 (3H, s, (CH_3)$_{2B}$), 1.44 (9H, s, C(CH_3)$_3$), 1.52 (1H, m, NHCHCH$_2$CH_{2A}), 1.61 (1H, m, NHCHCH$_2$CH_{2B}), 1.80 (1H, m, NHCHCH_{2A}CH$_2$), 2.01 (1H, m, NHCHCH_{2B}CH$_2$), 2.69 (1H, dd, *J* 7 and 5.5, NHCH(CH$_2$)$_2$-C*H*), 3.75 (3H, s, CO_2CH_3), 4.35 (1H, br m, NHC*H*CO_2CH_3) and 5.20 (1H, br d, *J* 8, NH); δ_C (125 MHz; $CDCl_3$) 18.61 and 18.62 ((CH_3)$_{2A}$), 24.77 and 24.79 (NHCHCH$_2$*C*H$_2$), 24.81 and 25.08 ((CH_3)$_{2B}$), 28.30 (C(*C*H_3)$_3$), 29.51 and 29.61 (NHCH*C*H$_2$CH$_2$), 52.30 and 52.36 ((CH$_3$)$_2$*C*CH), 53.08 and 53.27 ((NH*C*HCH$_2$), 58.55 (CO_2*C*H_3), 63.36 and 63.48 ((CH$_3$)$_2$*C*), 79.87 (*C*(CH_3)$_3$), 155.38 (OC(O)NH) and 173.01 (NHCH*C*O_2CH_3); HRMS 288.1823 (MH^+, $C_{14}H_{26}NO_5$ requires 288.1811 (δ 4.2 ppm)); *m*/*z* (Electrospray-MS) 288 (91%) and 232 (100%).

(2*S*)-2-*tert*-Butoxycarbonylamino-4,4-dimethylhexanoic acid methyl ester 15

Following the general procedure for alkene hydrogenation, (2*S*)-2-*tert*-butoxycarbonylamino-4,4-dimethylhex-5-enoic acid methyl ester **12** (93 mg, 0.34 mmol) yielded on purification by flash column chromatography over silica gel, eluting with EtOAc–heptane (1:5, v/v), (2*S*)-2-*tert*-butoxycarbonylamino-4,4-dimethylhexanoic acid methyl ester **15** (90 mg, 96%) as a colourless oil. Analytical HPLC t_r = 22.55 min (100%); $[\alpha]_D^{18}$ −6.1 (*c* 0.99 in CH_2Cl_2); δ_H (500 MHz; $CDCl_3$) 0.81 (3H, t, *J* 7.5, CH_3CH$_2$), 0.89 (3H, s, CH$_3$CH$_2$C(CH_3)$_{2A}$), 0.90 (3H, s, CH$_3$CH$_2$C(CH_3)$_{2B}$), 1.29 (2H, dq, *J* 7.5 and 1, CH$_3$CH_2), 1.38 (1H, dd, *J* 14.5 and 9, NHCHCH_{2A}), 1.42 (9H, s, C(CH_3)$_3$), 1.69 (1H, dd, *J* 14.5 and 3.5, NHCHCH_{2B}), 3.71 (3H, s, CO_2CH_3), 4.31 (1H, br m, NHC*H*CO_2CH_3) and 4.78 (1H, br d, *J* 8.5, NH); δ_C (125 MHz; $CDCl_3$) 8.66 (*C*H$_3$CH$_2$), 26.61 (CH$_3$-CH$_2$C(*C*H$_3$)$_2$), 28.28 (C(*C*H$_3$)$_3$), 33.06 (CH$_3$CH$_2$*C*(CH$_3$)$_2$), 34.40 (CH$_3$*C*H$_2$), 43.97 (NHCH*C*H$_2$), 50.84 ((NH*C*HCH$_2$), 52.13 (CO_2*C*H$_3$), 79.79 (*C*(CH_3)$_3$), 155.08 (OC(O)NH) and 174.46 (NHCH*C*O_2CH_3); HRMS 296.1827 (MNa, $C_{14}H_{27}NO_4Na$ requires 296.1838 (δ 3.7 ppm)); *m*/*z* (Electrospray-MS) 274 (69%) and 218 (100%).

(2*S*)-2-*tert*-Butoxycarbonylamino-4,4-dimethylhexanoic acid. Following the general procedure for methyl ester saponification, (2*S*)-2-*tert*-butoxycarbonylamino-4,4-dimethylhexanoic acid methyl ester **15** (90 mg, 0.33 mmol) gave (2*S*)-2-*tert*-butoxycarbonylamino-4,4-dimethylhexanoic acid (79 mg, 93%) as crystals which were used directly in the subsequent reaction. Analytical HPLC t_r = 20.90 min (100%); *m*/*z* (Electrospray-MS) 260 (33%) and 204 (100%).

(2*S*)-2-Amino-4,4-dimethylhexanoic acid hydrochloride salt. Following the general procedure of *N*-Boc removal using 4 M HCl in dioxane, (2*S*)-2-*tert*-butoxycarbonylamino-4,4-dimethylhexanoic acid (79 mg, 0.31 mmol) gave (2*S*)-2-amino-4,4-dimethylhexanoic acid hydrochloride salt (60 mg, 100%) as a solid, and was used directly in the subsequent reaction; *m*/*z* (Electrospray-MS) 160 (100%).

(2*S*)-2-(9*H*-Fluoren-9-ylmethoxycarbonylamino)-4,4-dimethylhexanoic acid 4

Following the general procedure for Fmoc protection of an amine, (2*S*)-2-amino-4,4-dimethylhexanoic acid hydrochloride salt (60 mg, 0.31 mmol) gave on purification by flash chromatography over silica gel, eluting with $CHCl_3$–CH_3OH (100:0 to 96:4, v/v), (2*S*)-2-(9*H*-fluoren-9-ylmethoxycarbonylamino)-4,4-dimethylhexanoic acid **4** (63 mg, 54%) as an amorphous solid, mp 64–65 °C. Analytical HPLC t_r = 23.63 min (100%); $[\alpha]_D^{18}$ −17.4 (*c* 1.01 in CH_2Cl_2); δ_H (500 MHz; $CDCl_3$) 0.82 (3H, t, *J* 7.5, CH_3CH$_2$), 0.91 (3H, s, CH$_3$CH$_2$C(CH_3)$_{2A}$), 0.92 (3H, s, CH$_3$CH$_2$C(CH_3)$_{2B}$), 1.29 (2H, br q, *J* 7.5, CH$_3$CH_2), 1.46 (1H, dd, *J* 14.5 and 9.5, NHCHCH_{2A}), 1.83 (1H, dd, *J* 14.5 and 2, NHCHCH_{2B}), 4.20 (1H, t, *J* 7, H-9′), 4.40 (3H, br m, NHC*H*CO_2H and CH$_2$O), 5.07 (1H, br d, *J* 7.5, NH), 7.28 (2H, m, H-2′ and H-7′), 7.37 (2H, m, H-3′ and H-6′), 7.56 (2H, m, H-1′ and H-8′) and 7.74 (2H, d, *J* 7.5, H-4′ and H-5′); δ_C (125 MHz; $CDCl_3$) 8.23 (*C*H$_3$CH$_2$), 26.62 (CH$_3$CH$_2$-C(*C*H$_3$)$_2$), 33.20 (CH$_3$CH$_2$*C*(CH$_3$)$_2$), 34.37 (CH$_3$*C*H$_2$), 43.40 (NHCH*C*H$_2$), 47.14 (CH-9′), 51.30 (NH*C*HCO$_2$H), 67.01 (CH$_2$O), 119.92 (CH-4′ and CH-5′), 124.99 (CH-1′ and CH-8′), 127.01 (CH-2′ and CH-7′), 127.65 (CH-3′ and CH-6′), 141.27 (C-4a′ and C-5a′), 143.70 (C-1a′ and C-8a′), 155.90

(OC(O)NH) and 177.07 (NHCHCO_2H); HRMS 404.1839 (MNa, $C_{23}H_{27}NO_4Na$ requires 404.1838 (δ 0.2 ppm)); *m/z* (Electrospray-MS) 382 (100%).

(2*S*)-2-*tert*-Butoxycarbonylamino-6-methylhept-5-enoic acid methyl ester 11

Hexachlorotungsten (106 mg, 0.30 mmol, 1.4 eq.) was weighed out into a Schlenk tube under nitrogen and dry THF (0.5 cm^3) was added. A solution of n-BuLi (0.216 cm^3, 2.5 M, 0.60 mmol, 2.8 eq.) was added dropwise at −78 °C and the solution was then left to warm up slowly to room temperature to give a clear brown solution. It was then recooled to −78 °C and treated with a solution of (2*S*)-2-*tert*-butoxycarbonylamino-4-[(2*S*)-3,3-dimethyloxiranyl]butyric acid methyl ester **13a** and (2*S*)-2-*tert*-butoxycarbonylamino-4-[(2*R*)-3,3-dimethyloxiranyl]-butyric acid methyl ester **13b** (55 mg, 0.19 mmol) in THF (0.2 cm^3). The reaction mixture was stirred at 0–5 °C for 30 min and then at room temperature for 1 h to give a clear green solution. The reaction mixture was poured into a 1 : 1 solution of 1.5 M sodium tartrate and 2 M sodium hydroxide (5 cm^3). The organic layer was removed and dried over magnesium sulfate, filtered and the solvent removed *in vacuo* to give a crude oil. The residue was purified by flash chromatography over silica gel eluting with EtOAc–heptane (1 : 5, v/v) to give (2*S*)-2-*tert*-butoxycarbonylamino-6-methylhept-5-enoic acid methyl ester **11** (25 mg, 48%) as a colourless oil. Analytical HPLC t_r = 21.32 min (100%); ν_{max}(film)/cm^{-1} 3364 (m), 2977 (m), 1744 (s), 1715 (s), 1516 (s) and 1167 (s); $[\alpha]_D^{18}$ +11.9 (*c* 1.01 in CH_2Cl_2); δ_H (500 MHz; $CDCl_3$) 1.43 (9H, s, $C(CH_3)_3$), 1.59 (3H, s, $(CH_3)_{2A}C$=CH), 1.64 (1H, m, NHCHCH$_2$CH_{2A}), 1.68 (3H, s, $(CH_3)_{2B}C$=CH), 1.82 (1H, m, NHCHCH$_2$CH_{2B}), 2.01 (1H, dd, *J* 14.5 and 7.5, NHCHCH_{2A}), 2.06 (1H, dd, *J* 14.5 and 6.5, NHCHCH_{2B}), 3.73 (3H, s, CO_2CH_3), 4.30 (1H, br m, NHC*H*-CO_2CH_3), 4.99 (1H, br d, *J* 7.0, NH) and 5.07 (1H, br t, *J* 7.0, $(CH_3)_2C$=C*H*); δ_C (125 MHz; $CDCl_3$) 17.65 ($(CH_3)_{2A}C$=CH), 23.89 (NHCHCH$_2$CH$_2$), 25.71 ($(CH_3)_{2B}C$=CH), 28.33 (C-$(CH_3)_3$), 32.67 (NHCHCH$_2$), 52.19 (CO_2CH_3), 53.15 (NH*C*H-CO_2CH_3), 79.53 ($C(CH_3)_3$), 122.68 ($(CH_3)_2C$=*C*H), 132.89 ($(CH_3)_2C$=CH), 155.21 (OC(O)NH) and 173.24 (NHCH-CO_2CH_3); HRMS 294.1687 (MNa, $C_{14}H_{25}NO_4Na$ requires 294.1681 (δ 1.8 ppm)); *m/z* (Electrospray-MS) 272 (100%).

(2*S*)-2-*tert*-Butoxycarbonylamino-6-methylheptanoic acid methyl ester 14

Following the general procedure for alkene hydrogenation, (2*S*)-2-*tert*-butoxycarbonylamino-6-methylhept-5-enoic methyl ester **11** (48 mg, 0.18 mmol) yielded on purification by flash column chromatography over silica gel, eluting with EtOAc–heptane (1 : 10, v/v), (2*S*)-*tert*-butoxycarbonylamino-6-methyl-heptanoic acid methyl ester **14** (48 mg, 100%) as a colourless oil. Analytical HPLC t_r = 22.65 min (100%); $[\alpha]_D^{23}$ −13.3 (*c* 0.96 in CH_3OH); δ_H (500 MHz; $CDCl_3$) 0.85 (6H, d, *J* 6.5, $(CH_3)_2$-CH), 1.16 (2H, m, NHCH(CH$_2$)$_2$CH_2), 1.30 (2H, m, NHCH-CH$_2$CH_2), 1.42 (9H, s, $C(CH_3)_3$), 1.51 (1H, qt, *J* 7 and 6.5, $(CH_3)_3CH$), 1.58 (1H, m, NHCHCH_{2A}), 1.74 (1H, m, NHCH-CH_{2B}), 3.71 (3H, s, CO_2CH_3), 4.28 (1H, br m, NHC*H*CO_2CH_3) and 4.99 (1H, br d, *J* 7.5, NH); δ_C (125 MHz; $CDCl_3$) 22.42 ($(CH_3)_{2A}CH$), 22.48 ($(CH_3)_{2B}CH$), 23.01 (NHCHCH$_2$CH$_2$), 27.72 ($(CH_3)_2CH$), 28.27 ($C(CH_3)_3$), 32.94 (NHCHCH$_2$), 38.33 (NHCH(CH$_2$)$_2$CH$_2$), 52.13 (CO_2CH_3), 53.39 (NH*C*H-CO_2CH_3), 155.32 (OC(O)NH) and 173.51 (NHCHCO_2CH_3); HRMS 296.1836 (MNa, $C_{14}H_{27}NO_4Na$ requires 296.1838 (δ 0.7 ppm)); *m/z* (Electrospray-MS) 274 (53%) and 218 (100%).

(2*S*)-2-*tert*-Butoxycarbonylamino-6-methylheptanoic acid. Following the general procedure for methyl ester saponification, (2*S*)-*tert*-butoxycarbonylamino-6-methylheptanoic acid methyl ester **14** (100 mg, 0.37 mmol) gave (2*S*)-2-*tert*-butoxycarbonyl-amino-6-methylheptanoic acid (88 mg, 92%) as a solid, and was used directly in the subsequent reaction. Analytical HPLC t_r = 20.04 min (100%); *m/z* (Electrospray-MS) 260 (8%) and 204 (100%).

(2*S*)-2-Amino-6-methylheptanoic acid hydrochloride salt. Following the general procedure of *N*-Boc removal using 4 M HCl in dioxane, (2*S*)-2-*tert*-butoxycarbonylamino-6-methyl-heptanoic acid (88 mg, 0.34 mmol) gave (2*S*)-2-amino-6-methylheptanoic acid hydrochloride salt (66 mg, 100%) as a solid and was used directly in the subsequent reaction; *m/z* (Electrospray-MS) 160 (100%).

(2*S*)-2-(9*H*-Fluoren-9-ylmethoxycarbonylamino)-6-methylhept-anoic acid 3

Following the general procedure for Fmoc protection of an amine (2*S*)-2-amino-6-methylheptanoic acid hydrochloride salt (66 mg, 0.34 mmol) gave on purification by flash chromatography over silica gel eluting with $CHCl_3$–CH_3OH (100 : 0 to 95 : 5, v/v), (2*S*)-2-(9*H*-fluoren-9-ylmethoxycarbonylamino)-6-methylheptanoic acid **3** (70 mg, 54%) as amorphous solid, mp 97–98 °C. Analytical HPLC t_r = 23.55 min (100%); $[\alpha]_D^{23}$ −14.6 (*c* 0.74 in CH_3OH); δ_H (500 MHz; $CDCl_3$) 0.84 (6H, d, *J* 7, $(CH_3)_2$CH), 1.09 (2H, br m, NHCH(CH$_2$)$_2$CH_2), 1.28 (2H, m, NHCHCH$_2$CH_2), 1.46 (1H, qt, *J* 7 and 6.5, $(CH_3)_3CH$), 1.63 (1H, m, NHCHCH_{2A}), 1.84 (1H, m, NHCHCH_{2B}), 4.18 (1H, t, *J* 7, H-9′), 4.36 (1H, br m, NHC*H*CO_2H), 4.38 (2H, d, *J* 6.5, CH_2O), 5.27 (1H, br d, *J* 8, NH), 7.28 (2H, m, H-2′ and H-7′), 7.37 (2H, m, H-3′ and H-6′), 7.57 (2H, m, H-1′ and H-8′) and 7.74 (2H, d, *J* 7.5, H-4′ and H-5′); δ_C (125 MHz; $CDCl_3$) 22.43 ($(CH_3)_{2A}CH$), 22.53 ($(CH_3)_{2B}CH$), 23.04 (NHCHCH$_2$CH$_2$), 27.71 ($(CH_3)_2CH$), 32.44 (NHCHCH$_2$), 38.29 (NHCH-(CH$_2$)$_2$CH$_2$), 47.09 (CH-9′), 53.83 (NH*C*HCO$_2$H), 67.05 (CH_2O), 119.95 (CH-4′ and CH-5′), 125.02 (CH-1′ and CH-8′), 127.03 (CH-2′ and CH-7′), 127.68 (CH-3′ and CH-6′), 141.26 (C-4a′ and C-5a′), 143.65 (C-1a′ and C-8a′), 156.10 (OC(O)NH) and 176.90 (NHCHCO_2H); HRMS 404.1856 (MNa, $C_{23}H_{27}NO_4Na$ requires 404.1838 (δ 4.4 ppm)); *m/z* (Electrospray-MS) 382 (100%) and 267 (70%).

(2*S*,4*R*)-2-*tert*-Butoxycarbonylamino-4,5-dimethylhex-5-enoic acid methyl ester 16a and (2*S*,4*S*)-2-*tert*-butoxycarbonylamino-4,5-dimethylhex-5-enoic acid methyl ester 16b

Using the general procedure for the coupling reaction (on six times the scale), toluene-4-sulfonic acid (*E*)-2-methylbut-2-enyl ester (3 ml, 1.8 M solution in DMF, 5.4 mmol) was coupled to the zinc reagent **1**, derived from *N*-(*tert*-butoxycarbonyl)-3-iodo-L-alanine methyl ester (1.48 g, 4.5 mmol) and zinc (900 mg, 13.8 mmol), in the presence of CuBr·DMS (126 mg, 0.60 mmol) to give a residue. ^{1}H NMR spectroscopy indicated that a 1 : 1 ratio of diastereoisomers had been obtained. This residue was purified by flash chromatography over silica gel, eluting with EtOAc–petroleum ether (1 : 9, v/v), to give three fractions, the first being (2*S*,4*R*)-2-*tert*-butoxycarbonylamino-4,5-dimethylhex-5-enoic acid methyl ester **16a** (136 mg, 11%), the second a mixed fraction of **16a** and **16b** (560 mg, 46%), and the third (2*S*,4*S*)-2-*tert*-butoxycarbonylamino-4,5-dimethylhex-5-enoic acid methyl ester **16b** (70 mg, 6%). The mixed fractions could be separated by further chromatography.

Diastereoisomer **16a** was a colourless oil. Analytical HPLC t_r = 22.52 min (90%); $[\alpha]_D^{20}$ +12.3 (*c* 1.06 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3382 (m), 3070 (m), 2966 (s), 1746 (s), 1716 (s), 1616 (w), 1507 (s) and 886 (m); δ_H (500 MHz; $CDCl_3$) 1.06 (3H, d, *J* 7, CH_3CH), 1.45 (9H, s, $C(CH_3)_3$), 1.58 (1H, m, CH_2=C-(CH$_3$)C*H*), 1.68 (3H, s, CH_2=C(CH_3)), 1.85 (1H, m, NHCH-CH_{2A}), 1.97 (1H, m, NHCHCH_{2B}), 3.73 (3H, s, CO_2CH_3), 4.29 (1H, m, NHC*H*CO_2CH_3), 4.72 (1H, s, CH_{2A}=C(CH$_3$)), 4.95 (1H, d, *J* 1.5, CH_{2B}=C(CH$_3$)) and 5.04 (1H, br d, *J* 7, NH); δ_C (125 MHz; $CDCl_3$) 18.61 (CH_2=C(*C*H$_3$)), 21.64 (CH_2=C-

(CH_3)CH(CH_3)), 28.32 (C(CH_3)$_3$), 30.79 (CH_2=C(CH_3)CH), 38.06 (NHCHCH_2), 52.00 (NHCHCO$_2$CH$_3$), 52.22 (CO$_2$$CH_3$), 79.53 ($C$($CH_3$)$_3$), 110.19 ($CH_2$=C($CH_3$)), 144.62 ($CH_2$=$C$($CH_3$)), 155.18 (OC(O)NH) and 173.30 (NHCHCO$_2$CH$_3$); HRMS 294.1684 (MNa, $C_{14}H_{25}NO_4Na$ requires 294.1681 (δ 0.8 ppm)); *m*/*z* (Electrospray-MS) 272 (26%) and 216 (100%).

Diastereoisomer **16b** was isolated as a colourless oil. Analytical HPLC t_r = 22.49 min (95%); $[a]_D^{20}$ +16.0 (*c* 0.60 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3369 (s), 3073 (m), 2969 (s), 1747 (s), 1717 (s), 1617 (w), 1517 (s) and 893 (m); δ_H (500 MHz; $CDCl_3$) 1.04 (3H, d, *J* 7, CH_3CH), 1.44 (9H, s, C(CH_3)$_3$), 1.55 (1H, m, CH_2=C(CH_3)CH), 1.67 (3H, s, CH_2=C(CH_3)), 1.91 (1H, m, NHCHCH_{2A}), 2.32 (1H, m, NHCHCH_{2B}), 3.72 (3H, s, CO$_2$CH$_3$), 4.26 (1H, m, NHCHCO$_2$CH$_3$), 4.75 (1H, d, *J* 1.5, CH_{2A}=C(CH_3)), 4.79 (1H, d, *J* 1.5, CH_{2B}=C(CH_3)) and 5.46 (1H, br d, *J* 6, NH); δ_C (125 MHz; $CDCl_3$) 18.51 (CH_2=C(CH_3)), 20.14 (CH_2=C(CH_3)CH(CH_3)), 28.31 (C(CH_3)$_3$), 30.55 (CH_2=C(CH_3)CH), 37.64 (NHCHCH_2), 52.17 (NHCH-CO$_2$CH$_3$), 52.22 (CO$_2$$CH_3$), 79.74 ($C$($CH_3$)$_3$), 111.27 ($CH_2$=C($CH_3$)), 147.94 ($CH_2$=$C$($CH_3$)), 155.36 (OC(O)NH) and 173.83 (NHCHCO$_2$CH$_3$); HRMS 294.1673 (MNa, $C_{14}H_{25}$-NO_4Na requires 294.1681 (δ 2.9 ppm)); *m*/*z* (Electrospray-MS) 272 (73%) and 216 (100%).

Compound **16b** was converted into the corresponding *N*-acetyl derivative, which exhibited a signal at δ 111.27 in the ^{13}C NMR spectrum , while the signal for the *N*-acetyl derivative of **16a** (prepared as a mixture with the *N*-acetyl derivative of **16b**) was at δ 110.2. These shifts compare very well with shifts of δ 111.1 and 110.1 reported for the tentatively assigned *syn*- and *anti*-*N*-acetyl analogues, respectively.[15]

(2*S*,4*R*)-2-*tert*-Butoxycarbonylamino-4,5-dimethylhexanoic acid methyl ester 17a and (2*S*,4*S*)-2-*tert*-butoxycarbonylamino-4,5-dimethylhexanoic acid methyl ester 17b

Following the general procedure for alkene hydrogenation, the first eluted diastereoisomer of (2*S*,4*R*)-2-*tert*-butoxycarbonylamino-4,5-dimethylhex-5-enoic acid methyl ester **16a** (63 mg, 0.23 mmol) yielded (2*S*,4*R*)-2-*tert*-butoxycarbonylamino-4,5-dimethylhexanoic acid methyl ester **17a** (60 mg, 95%) as a colourless oil. Analytical HPLC t_r = 22.52 min (90%); $[a]_D^{18}$ +3.3 (*c* 0.60 in CH_2Cl_2); δ_H (500 MHz; $CDCl_3$) 0.81 (3H, d, *J* 7, (CH_3)$_{2A}$CH), 0.84 (3H, d, *J* 7, (CH_3)$_2$CHCH(CH_3)), 0.87 (3H, d, *J* 7, (CH_3)$_{2B}$CH), 1.10 (1H, m, (CH_3)$_2$CH), 1.31 (1H, m, (CH_3)$_2$CHCH(CH_3)), 1.43 (9H, s, C(CH_3)$_3$), 1.53 (1H, m, NHCHCH_{2A}), 1.75 (1H, m, NHCHCH_{2B}), 3.72 (3H, s, CO$_2$CH$_3$), 4.26 (1H, br m, NHCHCO$_2$CH$_3$) and 4.96 (1H, br d, *J* 7, NH); HRMS 296.1835 (MNa, $C_{14}H_{27}NO_4Na$ requires 296.1838 (δ 1.0 ppm)); *m*/*z* (Electrospray-MS) 274 (43%) and 218 (100%).

Following the general procedure for alkene hydrogenation, the second eluted diastereoisomer of (2*S*,4*S*)-2-*tert*-butoxycarbonylamino-4,5-dimethylhex-5-enoic acid methyl ester **16b** (39 mg, 0.14 mmol) yielded (2*S*,4*S*)-2-*tert*-butoxycarbonylamino-4,5-dimethylhexanoic acid methyl ester **17b** (39 mg, 100%) as a colourless oil. Analytical HPLC t_r = 22.49 min (98%); $[a]_D^{18}$ + 32.0 (*c* 0.10 in CH_2Cl_2); δ_H (500 MHz; $CDCl_3$) 0.78 (3H, d, *J* 7, (CH_3)$_{2A}$CH), 0.84 (3H, d, *J* 7, (CH_3)$_2$-CHCH(CH_3)), 0.85 (3H, d, *J* 7, (CH_3)$_{2B}$CH), 1.37 (1H, m, NHCHCH_{2A}), 1.43 (9H, s, C(CH_3)$_3$), 1.52 (1H, m, (CH_3)$_2$CH-CH(CH_3)), 1.64 (1H, m, (CH_3)$_2$CH), 1.76 (1H, ddd, *J* 10, 7 and 6, NHCHCH_{2B}), 3.72 (3H, s, CO$_2$CH$_3$), 4.29 (1H, br m, NHCHCO$_2$CH$_3$) and 4.94 (1H, br d, *J* 7, NH); δ_C (125 MHz; $CDCl_3$) 15.16 ((CH_3)$_2$CHCH(CH_3)), 17.07 ((CH_3)$_{2A}$CH), 20.00 ((CH_3)$_{2B}$CH), 28.26 (C(CH_3)$_3$), 31.03 (CH_3)$_2$CH-CH(CH_3)), 34.66 (CH_3)$_2$CHCH(CH_3)), 37.53 (NHCHCH_2), 52.04 (NHCHCO$_2$CH$_3$), 52.12 (CO$_2$$CH_3$), 79.78 ($C$($CH_3$)$_3$), 155.17 (OC(O)NH) and 173.89 (NHCHCO$_2$CH$_3$); HRMS 296.1830 (MNa, $C_{14}H_{27}NO_4Na$ requires 296.1838 (δ 2.7 ppm)); *m*/*z* (Electrospray-MS) 274 (40%) and 218 (100%).

(2*S*,4*R*)-2-*tert*-Butoxycarbonylamino-4,5-dimethylhexanoic acid and (2*S*,4*S*)-2-*tert*-butoxycarbonylamino-4,5-dimethylhexanoic acid.

Following the general procedure for methyl ester saponification (2*S*,4*R*)-2-*tert*-butoxycarbonylamino-4,5-dimethylhexanoic acid methyl ester (60 mg, 0.22 mmol) yielded (2*S*,4*R*)-2-*tert*-butoxycarbonylamino-4,5-dimethylhexanoic acid (52 mg, 91%) as a colourless oil and was used directly in the subsequent reaction. Analytical HPLC t_r = 20.65 min (100%); *m*/*z* (Electrospray-MS) 260 (18%) and 204 (100%).

Following the general procedure for methyl ester saponification (2*S*,4*S*)-2-*tert*-butoxycarbonylamino-4,5-dimethylhexanoic acid methyl ester (32 mg, 0.12 mmol) yielded (2*S*,4*S*)-2-*tert*-butoxycarbonylamino-4,5-dimethylhexanoic acid (30 mg, 100%) as a colourless oil and was used directly in the subsequent reaction. Analytical HPLC t_r = 20.45 min (100%); *m*/*z* (Electrospray-MS) 260 (20%) and 204 (100%).

(2*S*,4*R*)-2-Amino-4,5-dimethylhexanoic acid hydrochloride salt and (2*S*,4*S*)-2-amino-4,5-dimethylhexanoic acid hydrochloride salt.

Following the general procedure of *N*-Boc removal using 4 M HCl in dioxane, (2*S*,4*R*)-2-*tert*-butoxycarbonylamino-4,5-dimethylhexanoic acid (52 mg, 0.20 mmol) yielded (2*S*,4*R*)-2-amino-4,5-dimethylhexanoic acid hydrochloride salt (39 mg, 100%) as a solid and was used directly in the subsequent reaction; *m*/*z* (Electrospray-MS) 160 (76%) and 142 (100%).

Following the general procedure of *N*-Boc removal using 4 M HCl in dioxane, (2*S*,4*S*)-2-*tert*-butoxycarbonylamino-4,5-dimethylhexanoic acid (32 mg, 0.12 mmol) yielded (2*S*,4*S*)-2-amino-4,5-dimethylhexanoic acid hydrochloride salt (24 mg, 100%) as a solid and was used directly in the subsequent reaction; *m*/*z* (Electrospray-MS) 160 (80%) and 142 (100%).

(2*S*,4*R*)-2-(9*H*-Fluoren-9-ylmethoxycarbonylamino)-4,5-dimethylhexanoic acid 5a and (2*S*,4*S*)-2-(9*H*-fluoren-9-ylmethoxycarbonylamino)-4,5-dimethylhexanoic acid 5b

Following the general procedure for Fmoc protection of an amine, (2*S*,4*R*)-2-amino-4,5-dimethylhexanoic acid hydrochloride salt (39 mg, 0.20 mmol) gave on purification by flash chromatography over silica gel, eluting with $CHCl_3$–CH_3OH (100:0 to 95:5, v/v), (2*S*,4*R*)-2-(9*H*-fluoren-9-ylmethoxycarbonylamino)-4,5-dimethylhexanoic acid **5a** (30 mg, 40%) as an amorphous solid, mp 53–54 °C. Analytical HPLC t_r = 23.46 min (100%); $[a]_D^{23}$ −10.4 (*c* 1.00 in CH_3OH); δ_H (500 MHz; $CDCl_3$) 0.85 (9H, m, (CH_3)$_2$CHCH(CH_3)), 1.34 (1H, m, (CH_3)$_2$-CHCH(CH_3)), 1.56 (1H, m, NHCHCH_{2A}), 1.64 (1H, br m, (CH_3)$_2$CHCH(CH_3)), 1.89 (1H, m, NHCHCH_{2B}), 4.21 (1H, t, *J* 7, H-9′), 4.41 (3H, m, CH_2O and NHCHCO$_2$H), 5.09 (1H, br d, *J* 7, NH), 7.29 (2H, m, H-2′ and H-7′), 7.39 (2H, m, H-3′ and H-6′), 7.56 (2H, m, H-1′ and H-8′) and 7.76 (2H, d, *J* 7, H-4′ and H-5′); HRMS 404.1825 (MNa, $C_{23}H_{27}NO_4Na$ requires 404.1838 (δ 3.2 ppm)); *m*/*z* (Electrospray-MS) 382 (100%).

Following the general procedure for Fmoc protection of an amine, (2*S*,4*S*)-2-amino-4,5-dimethylhexanoic acid hydrochloride salt (24 mg, 0.12 mmol) gave on purification by flash chromatography over silica gel, eluting with $CHCl_3$–CH_3OH (100:0 to 95:5, v/v), (2*S*,4*S*)-2-(9H-fluoren-9-ylmethoxycarbonylamino)-4,5-dimethylhexanoic acid **5b** (15 mg, 32%) as an amorphous solid, mp 50–51 °C. Analytical HPLC t_r = 23.23 min (100%); $[a]_D^{18}$ −12.8 (*c* 0.25 in CH_3OH); δ_H (500 MHz; $CDCl_3$) 0.80 (3H, d, *J* 6.5, (CH_3)$_{2A}$CH), 0.89 (6H, d, *J* 6.5, (CH_3)$_{2B}$CHCH(CH_3)), 1.49 (1H, m, NHCHCH_{2A}), 1.52 (1H, br m, (CH_3)$_2$CHCH(CH_3)), 1.66 (1H, br m, (CH_3)$_2$CHCH(CH_3)), 1.91 (1H, br m, NHCHCH_{2B}), 4.22 (1H, t, *J* 7, H-9′), 4.42 (3H, m, CH_2O and NHCHCO$_2$H), 5.13 (1H, br d, *J* 7, NH), 7.32 (2H, m, H-2′ and H-7′), 7.39 (2H, m, H-3′ and H-6′), 7.56 (2H, m, H-1′ and H-8′) and 7.76 (2H, d, *J* 7, H-4′ and H-5′); δ_C (125 MHz; $CDCl_3$) 15.08 ((CH_3)$_2$CHCH(CH_3)), 16.94

((CH_3)$_{2A}$CH), 20.10 ((CH_3)$_{2B}$CH), 30.94 ((CH_3)$_2$CHCH(CH_3)), 34.73 ((CH_3)$_2$CH*C*H(CH_3)), 37.13 (NHCH*C*H$_2$), 47.13 (CH-9′), 52.30 (NH*C*HCO$_2$H), 66.79 (CH_2O), 119.70 (CH-4′ and CH-5′), 124.78 (CH-1′ and CH-8′), 126.79 (CH-2′ and CH-7′), 127.44 (CH-3′ and CH-6′), 141.05 (C-4a′ and C-5a′), 143.61 (C-1a′ and C-8a′), 155.68 (OC(O)NH) and 178.00 (NHCH-*C*O$_2$H); HRMS 404.1841 (MNa, $C_{23}H_{27}NO_4Na$ requires 404.1838 (δ 0.7 ppm)); *m*/*z* (Electrospray-MS) 382 (100%).

(2*S*)-2-*tert*-Butoxycarbonylamino-5,6-dimethylhept-5-enoic acid methyl ester 18 and (2*S*)-2-*tert*-butoxycarbonylamino-4,4,5-trimethylhex-5-enoic acid methyl ester 19

Following the general procedure for zinc coupling reactions, 1-bromo-2,3-dimethylbut-2-ene (5.45 g, 33.46 mmol) was coupled to *N*-(*tert*-butoxycarbonyl)-3-iodo-L-alanine methyl ester (10.00 g, 30.40 mmol) in the presence of CuBr·DMS (0.80 g, 3.89 mmol) to give a residue which on purification by flash chromatography over silica gel eluting with EtOAc–heptane (1:9, v/v) gave two regioisomers in a ratio of 1:1 as established by ^{1}H NMR spectroscopy. The first eluted component was (2*S*)-2-*tert*-butoxycarbonylamino-5,6-dimethylhept-5-enoic acid methyl ester and further elution afforded (2*S*)-2-*tert*-butoxycarbonylamino-4,4,5-trimethylhex-5-enoic acid methyl ester. Fractions containing the initial component were pooled and reduced *in vacuo* to give (2*S*)-2-*tert*-butoxycarbonylamino-5,6-dimethylhept-5-enoic acid methyl ester **18** (2.51 g, 29%) as a colourless oil. Analytical HPLC t_r = 21.96 min (100%); $[\alpha]_D^{22}$ + 26.1 (*c* 1.02 in CH_2Cl_2) (Found: C, 63.1; H, 9.3; N, 4.9. $C_{15}H_{27}NO_4$ requires C, 63.1; H, 9.5; N, 4.9%); ν_{max}(film)/cm^{-1} 3366 (m), 3154 (m), 2978 (s), 1744 (s), 1718 (s), 1506 (s), 1366 (s) and 1164 (s); δ_H (500 MHz; $CDCl_3$) 1.43 (9H, s, C(CH_3)$_3$), 1.60 (9H, m, (CH_3)$_2$C=C(CH_3)), 1.66 (1H, m, NHCHCH_{2A}), 1.85 (1H, m, NHCHCH_{2B}), 2.00 (1H, ddd, *J* 13, 12.5 and 5, NHCHCH$_2$CH_{2A}), 2.07 (1H, ddd, *J* 13, 10.5 and 6, NHCH-CH$_2$CH_{2B}), 3.72 (3H, s, CO_2CH_3), 4.25 (1H, br m, NHC*H*-CO_2CH_3) and 5.00 (1H, br d, *J* 7, NH); δ_C (125 MHz; $CDCl_3$) 18.14 ((CH_3)$_2$C=C(*C*H$_3$)), 19.92 ((CH_3)$_{2A}$C=C(CH_3)), 20.53 ((CH_3)$_{2B}$C=C(CH_3)), 28.26 (C(*C*H$_3$)$_3$), 30.01 (NHCHCH$_2$*C*H$_2$), 30.86 (NHCH*C*H$_2$), 52.10 (OCH_3), 53.41 (NH*C*HCO$_2$CH$_3$), 79.74 (*C*(CH$_3$)$_3$), 125.36 ((CH_3)$_2$*C*=C(CH_3)), 125.93 ((CH_3)$_2$-C=*C*(CH_3), 155.30 (OC(O)NH) and 173.34 (NHCH*C*O$_2$CH$_3$); HRMS 308.1829 (MNa, $C_{15}H_{27}NO_4Na$ requires 308.1838 (δ 2.9 ppm)); *m*/*z* (Electrospray-MS) 286 (100%).

Pooling together the fractions containing the later-eluting component gave (2*S*)-2-*tert*-butyloxycarbonylamino-4,4,5-trimethylhex-5-enoic methyl ester **19** (2.60 g, 30%) as a colourless oil. Analytical HPLC t_r = 21.02 min (100%); $[\alpha]_D^{18}$ +3.5 (*c* 0.83 in CH_2Cl_2) (Found: C, 62.7; H, 9.3; N, 4.95. $C_{15}H_{27}NO_4$ requires C, 63.1; H, 9.5; N, 4.9%); ν_{max}(film)/cm^{-1} 3368 (s), 3091 (m), 2934 (s), 1748 (s), 1717 (s) and 1516 (s); δ_H (500 MHz; $CDCl_3$) 1.08 (3H, s, CH_2=C(CH_3)C(CH_{3A}), 1.10 (3H, s, CH_2=C-(CH_3)C(CH_{3B}), 1.40 (9H, s, C(CH_3)$_3$), 1.59 (1H, dd, *J* 14.5 and 9, NHCHCH_{2A}), 1.73 (3H, d, *J* 1, H_2C=C(CH_3)), 1.90 (1H, dd, *J* 14.5 and 4, NHCHCH_{2B}), 3.67 (3H, s, CO_2CH_3), 4.22 (1H, br m, NHC*H*CO$_2$CH$_3$), 4.77 (1H, d, *J* 1, CH_{2A}=C(CH_3)) and 4.81 (2H, br m, CH_{2B}=C(CH_3) and NH); δ_C (125 MHz; $CDCl_3$) 19.31 (CH_2=C(*C*H$_3$)), 27.13 (CH_2=CC(CH_3)C(*C*H$_3$)$_{2A}$), 27.54 (CH_2=CC(CH_3)C(*C*H$_3$)$_{2B}$), 28.28 (C(*C*H$_3$)$_3$), 38.45 ((CH_2=C(CH_3)*C*(CH_3)$_2$), 42.91 (NHCH*C*H$_2$), 51.29 (NH*C*HCO$_2$CH$_3$), 52.04 (CO_2CH_3), 79.64 (*C*(CH$_3$)$_3$), 110.88 (*C*H$_2$=C(CH_3)), 150.57 (CH_2=*C*(CH_3)), 154.96 (OC(O)NH) and 174.04 (NHCH-*C*O$_2$CH$_3$); HRMS 308.1838 (MNa, $C_{15}H_{27}NO_4Na$ requires 308.1838 (δ 2.2 ppm)); *m*/*z* (Electrospray-MS) 286 (100%).

(2*S*,5*S*)-2-*tert*-Butoxycarbonylamino-5,6-dimethylheptanoic acid methyl ester and (2*S*,5*R*)-2-*tert*-butoxycarbonylamino-5,6-dimethylheptanoic acid methyl ester 20

Following the general procedure for alkene hydrogenation, (2*S*)-2-*tert*-butoxycarbonylamino-5,6-dimethylhept-5-enoic methyl ester **18** (6.78 g, 23.79 mmol) yielded on purification by flash column chromatography over silica gel, eluting with EtOAc–heptane (1:9, v/v), an inseparable mixture of (2*S*,5*S*)-2-*tert*-butoxycarbonylamino-5,6-dimethylheptanoic acid methyl ester and (2*S*,5*R*)-2-*tert*-butoxycarbonylamino-5,6-dimethylheptanoic acid methyl ester **20** (6.63 g, 97%) as a colourless oil. Analytical HPLC t_r = 24.06 min (100%); $[\alpha]_D^{23}$ −12.1 (*c* 1.26 in CH_3OH) (Found: C, 62.9; H, 10.1; N, 4.9. $C_{15}H_{29}NO_4Na$ requires C, 62.7; H, 10.2; N, 4.9%); δ_H (500 MHz; $CDCl_3$) 0.76 (3H, dd, *J* 7 and 3.5, (CH_3)$_2$CHCH(CH_3)), 0.78 (3H, dd, *J* 7 and 1.5, (CH_{3A})$_2$CHCH(CH_3), 0.83 (3H, dd, *J* 7 and 1.5, (CH_{3B})$_2$CHCH(CH_3)), 1.09 (1H, m, NHCHCH$_2$CH_{2A}), 1.26 (1H, m, (CH_3)$_2$CHC*H*(CH_3)), 1.37 (1H, m, NHCHCH$_2$CH_{2B}), 1.42 (9H, s, C(CH_3)$_3$), 1.53 (1.5H, m, (CH_3)$_2$C*H*CH(CH_3) and 0.5 NHCHCH_{2A}), 1.63 (0.5H, m, 0.5 NHCHCH_{2A}), 1.74 (0.5H, br m, 0.5 NHCHCH_{2B}), 1.84 (0.5H, br m, 0.5 NHCHCH_{2B}), 3.72 (3H, s, CO_2CH_3), 4.25 (1H, br m, NHC*H*CO$_2$CH$_3$) and 4.99 (1H, br m, NH); δ_C (125 MHz; $CDCl_3$) 15.16 and 15.18 ((CH_3)$_2$CHCH(*C*H$_3$)), 17.78 and 17.91 ((CH_3)$_{2A}$CHCH(CH_3)), 20.06 and 20.14 ((CH_3)$_{2B}$CHCH(CH_3)), 28.26 (C(*C*H$_3$)$_3$), 29.38 and 29.47 (NHCHCH$_2$*C*H$_2$), 30.60 and 30.75 (NHCH*C*H$_2$), 31.66 and 31.83 ((CH_3)$_2$*C*HCH(CH_3)), 38.07 and 38.27 ((CH_3)$_2$-CH*C*H(CH_3)), 52.10 (NHCHCO$_2$*C*H$_3$), 53.55 and 53.68 (NH*C*HCO$_2$CH$_3$), 79.75 (*C*(CH$_3$)$_3$), 155.306 (OC(O)NH) and 173.43 and 173.49 (NHCH*C*O$_2$CH$_3$); HRMS 310.1982 (MNa, $C_{15}H_{29}NO_4Na$ requires 310.1994 (δ 4.1 ppm)); *m*/*z* (Electrospray-MS) 288 (68%) and 232 (74%).

(2*S*,5*S*)-2-*tert*-Butoxycarbonylamino-5,6-dimethylheptanoic acid and (2*S*,5*R*)-2-*tert*-butoxycarbonylamino-5,6-dimethylheptanoic acid 22

Following the general procedure for methyl ester saponification, (2*S*,5*S*)-2-*tert*-butoxycarbonylamino-5,6-dimethylheptanoic acid methyl ester and (2*S*,5*R*)-2-*tert*-butoxycarbonylamino-5,6-dimethylheptanoic acid methyl ester **20** (6.60 g, 23.00 mmol) gave after purification by flash chromatography over silica gel, eluting with $CHCl_3$–MeOH (95:5, v/v), (2*S*,5*S*)-2-*tert*-butoxycarbonylamino-5,6-dimethylheptanoic acid and (2*S*,5*R*)-2-*tert*-butoxycarbonylamino-5,6-dimethylheptanoic acid **22** (6.28 g, 100%) as a colourless oil. Analytical HPLC t_r = 21.44 min (100%); δ_H (500 MHz; $CDCl_3$) 0.79 (6H, d, *J* 6.5, (CH_3)$_{2A}$CH-CH(CH_3)), 0.84 (3H, d, *J* 7, (CH_{3B})$_2$CHCH(CH_3)), 1.15 (1H, m, NHCHCH$_2$CH_{2A}), 1.28 (1H, m, (CH_3)$_2$CHC*H*(CH_3)), 1.40 (1H, m, NHCHCH$_2$CH_{2B}), 1.44 (9H, s, C(CH_3)$_3$), 1.54 (1.5H, br m, (CH_3)$_2$C*H*CH(CH_3) and 0.5 NHCHCH_{2A}), 1.68 (0.5H, br m, 0.5 NHCHCH_{2A}), 1.79 (0.5H, br m, 0.5 NHCHCH_{2B}), 1.89 (0.5H, br m, 0.5 NHCHCH_{2B}), 4.25 (1H, br m, NHC*H*-CO_2CH_3) and 5.09 (1H, br s, NH); δ_C (125 MHz; $CDCl_3$) 15.12 ((CH_3)$_2$CHCH(*C*H$_3$)), 17.75 and 17.89 ((CH_3)$_{2A}$CHCH(CH_3)), 20.12 and 20.23 ((CH_3)$_{2B}$CHCH(CH_3)), 28.27 (C(*C*H$_3$)$_3$), 29.46 and 29.62 (NHCHCH$_2$*C*H$_2$), 30.30 and 30.48 (NHCH*C*H$_2$), 31.66 and 31.83 ((CH_3)$_2$*C*HCH(CH_3)), 38.09 and 38.34 ((CH_3)$_2$-CH*C*H(CH_3)), 53.81 and 53.99 (NH*C*HCO$_2$CH$_3$), 80.01 (*C*(CH$_3$)$_3$), 155.69 (OC(O)NH) and 177.61 (NHCH*C*O$_2$H); HRMS 296.1831 (MNa, $C_{14}H_{27}NO_4Na$ requires 296.1838 (δ 2.4 ppm)); *m*/*z* (Electrospray-MS) 274 (19%) and 218 (100%).

(2*S*,5*S*)-2-Amino-5,6-dimethylheptanoic acid hydrochloride salt and (2*S*,5*R*)-2-amino-5,6-dimethylheptanoic acid hydrochloride salt. Following the general procedure of *N*-Boc removal using 4 M HCl in dioxane, (2*S*,5*S*)-2-*tert*-butoxycarbonylamino-5,6-dimethylheptanoic acid and (2*S*,5*R*)-2-*tert*-butoxycarbonylamino-5,6-dimethylheptanoic acid (2.47 g, 9.05 mmol) gave (2*S*,5*S*)-2-amino-5,6-dimethylheptanoic acid hydrochloride salt and (2*S*,5*R*)-2-amino-5,6-dimethylheptanoic acid hydrochloride salt (1.84 g, 97%) as a solid and used in the subsequent reaction without further purification; *m*/*z* (Electrospray-MS) 174 (100%).

(2*S*,5*S*)-2-(9*H*-Fluoren-9-ylmethoxycarbonylamino)-5,6-dimethylheptanoic acid and (2*S*,5*R*)-2-(9*H*-fluoren-9-ylmethoxycarbonylamino)-5,6-dimethylheptanoic acid 6

Following the general procedure for Fmoc protection of an amine, (2*S*,5*S*)-2-amino-5,6-dimethylheptanoic acid hydrochloride salt and (2*S*,5*R*)-2-amino-5,6-dimethylheptanoic acid hydrochloride salt (1.84 g, 8.78 mmol) gave on purification by flash chromatography over silica gel eluting with $CHCl_3$–CH_3OH (100:0 to 95:5, v/v), (2*S*,5*S*)-2-(9*H*-fluoren-9-ylmethoxycarbonylamino)-5,6-dimethylheptanoic acid and (2*S*,5*R*)-2-(9*H*-fluoren-9-ylmethoxycarbonylamino)-5,6-dimethylheptanoic acid **6** (1.94 g, 56%) as an amorphous solid, mp 43–44 °C. Analytical HPLC t_r = 24.52 min (100%); δ_H (500 MHz; $CDCl_3$) 0.78 (6H, m, $(CH_3)_{2A}CHCH(CH_3)$), 0.84 (3H, d, *J* 6.5, $(CH_3)_{2B}CHCH(CH_3)$), 1.15 (1H, m, $NHCHCH_2CH_{2A}$), 1.29 (1H, m, $(CH_3)_2CHCH(CH_3)$), 1.40 (1H, m, $NHCHCH_2CH_{2B}$), 1.54 (1H, m, $(CH_3)_2CHCH(CH_3)$), 1.64 (0.5H, m, 0.5 $NHCHCH_{2A}$), 1.73 (0.5H, m, 0.5 $NHCHCH_{2A}$), 1.85 (0.5H, m, 0.5 $NHCHCH_{2B}$), 1.94 (0.5H, m, 0.5 $NHCHCH_{2B}$), 4.22 (1H, t, *J* 7, H-9′), 4.37 (1H, m, $NHCHCO_2H$), 4.41 (2H, br d, *J* 7, CH_2O), 5.29 (1H, br s, NH), 7.27 (2H, m, H-2′ and H-7′), 7.37 (2H, m, H-3′ and H-6′), 7.56 (2H, m, H-1′ and H-8′) and 7.75 (2H, d, *J* 7, H-4′ and H-5′); δ_C (125 MHz; $CDCl_3$) 15.12 ($(CH_3)_2CHCH(CH_3)$), 17.70 and 17.94 ($(CH_3)_{2A}CHCH(CH_3)$), 20.14 and 20.25 ($(CH_3)_{2B}CHCH(CH_3)$), 29.44 and 29.58 ($NHCHCH_2CH_2$), 30.26 and 30.39 ($NHCHCH_2$), 31.59 and 31.86 ($(CH_3)_2CHCH(CH_3)$), 38.10 and 38.28 ($(CH_3)_2CHCH(CH_3)$), 47.11 (CH-9′), 53.98 and 54.08 ($NHCHCO_2H$), 67.08 and 67.61 (CH_2O), 119.72 (CH-4′ and CH-5′), 124.80 (CH-1′ and CH-8′), 126.81 (CH-2′ and CH-7′), 127.46 (CH-3′ and CH-6′), 141.05 (C-4a′ and C-5a′), 143.47 (C-1a′ and C-8a′), 155.89 (OC(O)NH) and 177.19 ($NHCHCO_2H$); HRMS 418.1992 (MNa, $C_{24}H_{29}NO_4Na$ requires 418.1994 (δ 0.62 ppm)); *m*/*z* (Electrospray-MS) 396 (46%) and 267 (100%).

(2*S*)-2-*tert*-Butoxycarbonylamino-4,4,5-trimethylhexanoic acid methyl ester 21

Following the general procedure for alkene hydrogenation, (2*S*)-2-*tert*-butoxycarbonylamino-4,4,5-trimethylhex-5-enoic methyl ester **19** (5.85 g, 3.51 mmol) yielded on purification by flash column chromatography over silica gel, eluting with EtOAc–heptane (1:5, v/v), (2*S*)-2-*tert*-butoxycarbonylamino-4,4,5-trimethylhexanoic acid methyl ester **21** (5.60 g, 95%) as a colourless oil. Analytical HPLC t_r = 22.91 min (100%); $[\alpha]_D^{17}$ −5.7 (*c* 0.83 in CH_2Cl_2) (Found: C, 62.7; H, 10.0; N, 4.8. $C_{15}H_{29}NO_4$ requires C, 62.7; H, 10.2; N, 4.9%); δ_H (500 MHz; $CDCl_3$) 0.83 (3H, d, *J* 7, $(CH_3)_{2A}CHCH(CH_3)_2$), 0.84 (3H, d, *J* 7, $(CH_3)_{2B}CHCH(CH_3)_2$), 0.85 (3H, s, $(CH_3)_2CHCH(CH_3)_{2A}$), 0.89 (3H, s, $(CH_3)_2CHCH(CH_3)_{2B}$), 1.40 (1H, dd, *J* 14.5 and 9, $NHCHCH_{2A}$), 1.42 (9H, s, $C(CH_3)_3$), 1.54 (1H, q, *J* 7, $(CH_3)_2CH$), 1.72 (1H, dd, *J* 14.5 and 3, $NHCHCH_{2B}$), 3.71 (3H, s, CO_2CH_3), 4.34 (1H, br m, $NHCHCO_2CH_3$) and 4.79 (1H, br d, *J* 8, NH); δ_C (125 MHz; $CDCl_3$) 17.22 ($(CH_3)_{2A}CHCH(CH_3)_2$), 17.34 ($(CH_3)_{2B}CHCH(CH_3)_2$), 23.81 ($(CH_3)_2CHCH(CH_3)_{2A}$), 24.41 ($(CH_3)_2CHCH(CH_3)_{2B}$), 28.28 ($C(CH_3)_3$), 35.33 ($(CH_3)_2CHC(CH_3)_2$), 35.94 ($(CH_3)_2CHCH(CH_3)_2$), 42.67 ($NHCHCH_2$), 50.69 ($NHCHCO_2CH_3$), 52.14 (CO_2CH_3), 79.80 ($C(CH_3)_3$), 155.08 (OC(O)NH) and 174.57 ($NHCHCO_2CH_3$); HRMS 310.1987 (MNa, $C_{15}H_{29}NO_4Na$ requires 310.1994 (δ 2.4 ppm)); *m*/*z* (Electrospray-MS) 288 (48%) and 232 (100%).

(2*S*)-2-*tert*-Butoxycarbonylamino-4,4,5-trimethylhexanoic acid 23

Following the general procedure for methyl ester saponification, (2*S*)-2-*tert*-butoxycarbonylamino-4,4,5-trimethylhexanoic acid methyl ester **21** (5.60 g, 19.49 mmol) gave on purification by flash column chromatography over silica gel, eluting with $CHCl_3$–CH_3OH (95:5, v/v), (2*S*)-2-*tert*-butoxycarbonylamino-4,4,5-trimethylhexanoic acid **23** (5.33 g, 100%) as a colourless oil. Analytical HPLC t_r = 22.91 min (100%); $[\alpha]_D^{17}$ −19.1 (*c* 0.70 in CH_2Cl_2); δ_H (500 MHz; $CDCl_3$) 0.83 (6H, d, *J* 7, $(CH_3)_2CHCH(CH_3)_2$), 0.86 (3H, s, $(CH_3)_2CHCH(CH_3)_{2A}$), 0.90 (3H, s, $(CH_3)_2CHCH(CH_3)_{2B}$), 1.42 (9H, s, $C(CH_3)_3$), 1.43 (1H, m, $NHCHCH_{2A}$), 1.55 (1H, m, $(CH_3)_2CH$), 1.82 (1H, br d, *J* 14.5, $NHCHCH_{2B}$), 4.31 (1H, br m, $NHCHCO_2CH_3$) and 4.86 (1H, br d, *J* 8, NH); δ_C (125 MHz; $CDCl_3$) 17.23 ($(CH_3)_{2A}CHCH(CH_3)_2$), 17.36 ($(CH_3)_{2B}CHCH(CH_3)_2$), 23.82 ($(CH_3)_2CHCH(CH_3)_{2A}$), 24.44 ($(CH_3)_2CHCH(CH_3)_{2B}$), 28.30 ($C(CH_3)_3$), 35.41, 35.99 ($(CH_3)_2CHCH(CH_3)_2$), 42.42 ($NHCHCH_2$), 50.84 ($NHCHCO_2CH_3$), 80.12 ($C(CH_3)_3$), 155.44 (OC(O)NH) and 178.93 ($NHCHCO_2H$); HRMS 296.1826 (MNa, $C_{14}H_{27}NO_4Na$ requires 296.1838 (δ 4.1 ppm)); *m*/*z* (Electrospray-MS) 274 (38%) and 218 (100%).

(2*S*)-2-Amino-4,4,5-trimethylhexanoic acid hydrochloride salt. Following the general procedure of *N*-Boc removal using 4 M HCl in dioxane, (2*S*)-2-*tert*-butoxycarbonylamino-4,4,5-trimethylhexanoic acid (1.85 g, 6.80 mmol) gave (2*S*)-2-amino-4,4,5-trimethylhexanoic acid hydrochloride salt (1.42 g, 100%) as a solid; *m*/*z* (Electrospray-MS) 174 (100%).

(2*S*)-2-(9*H*-Fluoren-9-ylmethoxycarbonylamino)-4,4,5-trimethylhexanoic acid 7

Following the general procedure for Fmoc protection of an amine, (2*S*)-2-amino-4,4,5-trimethylhexanoic acid hydrochloride salt (1.42 g, 6.78 mmol) gave on purification by flash chromatography over silica gel eluting with $CHCl_3$–CH_3OH (100:0 to 95:5, v/v), (2*S*)-2-(9*H*-fluoren-9-ylmethoxycarbonylamino)-4,4,5-trimethylhexanoic acid **7** (1.23 g, 46%) as an amorphous solid, mp 61–62 °C. Analytical HPLC t_r = 24.28 min (100%); $[\alpha]_D^{17}$ −15.0 (*c* 0.62 in CH_2Cl_2); δ_H (500 MHz; $CDCl_3$) 0.85 (9H, m, $(CH_3)_2CHCH(CH_3)_{2A}$), 0.91 (3H, s, $(CH_3)_2CHCH(CH_3)_{2B}$), 1.46 (1H, dd, *J* 14 and 9, $NHCH_{2A}$), 1.54 (1H, m, $(CH_3)_2CH$), 1.88 (1H, dd, *J* 14 and 3, $NHCH_{2B}$), 4.21 (1H, t, *J* 6.5, H-9′), 4.40 (3H, br m, $NHCHCO_2H$ and CH_2O), 5.10 (1H, br d, *J* 7.5, NH), 7.27 (2H, m, H-2′ and H-7′), 7.36 (2H, m, H-3′ and H-6′), 7.57 (2H, m, H-1′ and H-8′) and 7.74 (2H, d, *J* 7, H-4′ and H-5′); δ_C (125 MHz; $CDCl_3$) 17.01 ($(CH_3)_{2A}CH$), 17.16 ($(CH_3)_{2B}CH$), 23.69 ($(CH_3)_2CHC(CH_3)_{2A}$), 24.27 ($(CH_3)_2CHC(CH_3)_{2B}$), 35.27 ($(CH_3)_2CHC(CH_3)_2$), 35.73 ($(CH_3)_2CH$), 41.88 ($NHCHCH_2$), 46.93 (CH-9′), 54.20 ($NHCHCO_2H$), 66.79 (CH_2O), 119.70 (CH-4′ and CH-5′), 124.78 (CH-1′ and CH-8′), 126.79 (CH-2′ and CH-7′), 127.44 (CH-3′ and CH-6′), 141.05 (C-4a′ and C-5a′), 143.61 (C-1a′ and C-8a′), 155.68 (OC(O)NH) and 178.00 ($NHCHCO_2H$); HRMS 418.1990 (MNa, $C_{24}H_{29}NO_4Na$ requires 418.1994 (δ 1.1 ppm)); *m*/*z* (Electrospray-MS) 396 (100%).

Acknowledgements

We thank Medivir (UK) for partial funding of a studentship (H. J. C. Deboves). We also thank Dr M. N. S. Hill, Mrs L. Cook, Mr D. Dunbar and Mr S. Addison for obtaining spectroscopic and other data, and Mr E. Hart for his invaluable technical assistance.

References

1 R. E. Babine and S. L. Bender, *Chem. Rev.*, 1997, **97**, 1359.
2 R. F. W. Jackson, N. Wishart, A. Wood, K. James and M. J. Wythes, *J. Org. Chem.*, 1992, **57**, 3397.
3 M. J. Dunn, R. F. W. Jackson, J. Pietruszka and D. Turner, *J. Org. Chem.*, 1995, **60**, 2210.
4 R. F. W. Jackson, R. J. Moore, C. S. Dexter, J. Elliott and C. E. Mowbray, *J. Org. Chem.*, 1998, **63**, 7875.
5 C. S. Dexter and R. F. W. Jackson, *Chem. Commun.*, 1998, 75.
6 J. Shoji and R. Sakazaki, *J. Antibiot.*, 1970, **23**, 519.
7 T. Shiba, Y. Mukunoki and H. Akiyama, *Bull. Chem. Soc. Jpn.*, 1975, **48**, 1902.

8 W. F. J. Karstens, M. Stol, F. Rutjes and H. Hiemstra, *Synlett*, 1998, 1126.
9 W. F. J. Karstens, M. J. Moolenaar, F. Rutjes, U. Grabowska, W. N. Speckamp and H. Hiemstra, *Tetrahedron Lett.*, 1999, **40**, 8629.
10 L. A. Paquette and G. D. Maynard, *J. Am. Chem. Soc.*, 1992, **114**, 5018.
11 M. A. Umbreit and K. B. Sharpless, *Org. Synth.*, 1981, **60**, 29.
12 M. L. Hill and R. A. Raphael, *Tetrahedron*, 1990, **46**, 4587.
13 W. J. E. Parr, *J. Chem. Res.* (*S*), 1981, 354.
14 M. J. Kurth and H. W. Decker, *J. Org. Chem.*, 1985, **50**, 5769.
15 J. V. Duncia, P. T. Lansbury, T. Miller and B. B. Snider, *J. Am. Chem. Soc.*, 1982, **104**, 1930.
16 J. J. McCullough, W. K. Macinnis, C. J. L. Lock and R. Faggiani, *J. Am. Chem. Soc.*, 1982, **104**, 4644.