ARTICLE

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Combined application of organozinc chemistry and one-pot hydroboration–Suzuki coupling to the synthesis of amino acids

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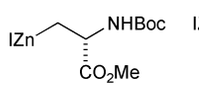
Hydroboration using 9-BBN-H of the protected enantiomerically pure but-3-enylglycine derivative **11**, prepared by copper-catalysed allylation of the serine-derived organozinc reagent **1**, followed by Suzuki coupling of the derived borane with a variety of aromatic halides, 2-bromopyridine and 2-bromopropene gives the protected amino acids **14a**–**l** and **15**. This method augments our previous methods for the synthesis of phenylalanine homologues.

Introduction

The synthesis of non-proteinogenic α-amino acids has been an area of great interest in recent years. Their use as building blocks in natural product and pharmaceutical synthesis has received considerable attention. Amongst the targets that have attracted substantial interest are amino acids which carry an aromatic residue on the side chain.

With these targets in mind, we have prepared a family of organozinc reagents **1**–**3** which can be coupled with aryl iodides under palladium-catalysis to produce a wide range of phenylalanine **4**,[1,2] homophenylalanine **5**[2] and bis-homophenylalanine derivatives **6**[2] in moderate to good yields. However, no direct route to the next higher homologue **7** has been reported so far.



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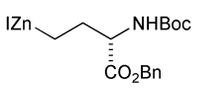

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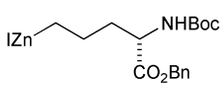

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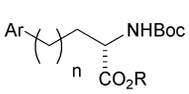
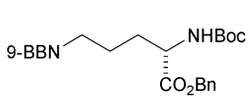


4, n = 0
5, n = 1
6, n = 2
7, n = 3

An alternative method for the synthesis of α-amino acids with aromatic side-chains using the hydroboration of protected unsaturated amino acids and the subsequent Suzuki coupling[3] of the intermediate organoboranes with aromatic halides has recently been described by Taylor's group. This approach works especially well for the synthesis of bis-homophenylalanine derivatives, *via* the borane **8** since the required starting material, allyl glycine, is easily available.[4,5] The synthesis of homophenylalanine derivatives can also be achieved, but in this case it is more effective to use the reduced derivative **9**, in order to avoid competing side-reactions.[6–8]



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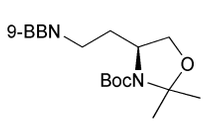
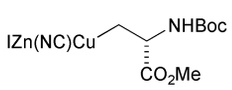


9

We showed some time ago that transmetallation of the organozinc reagent **1** to the zinc–copper reagent **10** with CuCN·2LiCl, followed by reaction with allyl chloride, gave enantiomerically pure but-3-enylglycine **11**.[9] It therefore appeared reasonable that application of the hydroboration–Suzuki methodology to this compound would provide a general solution to the synthesis of the phenylalanine homologues **7**. In this paper we describe the successful realisation of this goal.



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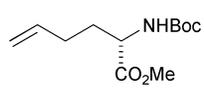
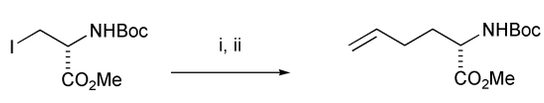


11

Results and discussion

Following our discovery that the reaction of the zinc reagent **1** with allylic electrophiles can be carried out using a catalytic amount of $CuBr{\cdot}SMe_2$,[10] as previously established for other organozinc reagents,[11] we employed this method in simple allylation. The organozinc reagent **1** was generated from the protected iodoalanine **12** using activated zinc dust in DMF. The excess zinc dust was allowed to settle and the supernatant was then removed by syringe and added to a pre-mixed DMF solution of $CuBr{\cdot}SMe_2$ (0.13 eq.) and allyl chloride at −15 °C (Scheme 1). After subsequent purification by flash chromatography the allylated compound **11** was isolated in 60% yield, which was obtained consistently on a 10 mmol scale. Not only is the work-up much simpler, but the yield is higher than we had previously obtained (51%) using CuCN·2LiCl.



12 **11**

Scheme 1 *Reagents and conditions:* (i) Zn* (prepared from Zn dust using I_2) in DMF. (ii) allyl chloride, $CuBr{\cdot}SMe_2$ (cat.), −15 °C.

Suzuki cross-coupling reactions

With protected but-3-enylglycine **11** in hand, we investigated the hydroboration–Suzuki coupling. Following the published procedure,[8] we carried out the hydroboration–Suzuki reactions with alkene **11** using a variety of electrophiles. In order to establish the best conditions to carry out the coupling, we chose to examine the hydroboration–Suzuki coupling using iodobenzene as an electrophile under a variety of conditions (Table 1, Scheme 2).

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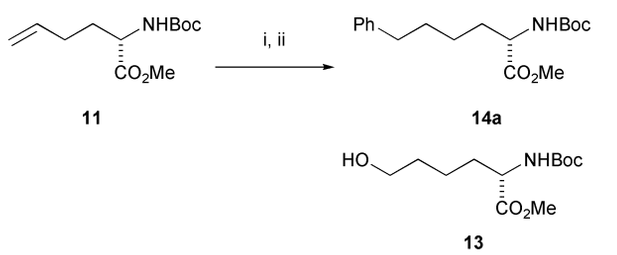
The hydroboration of alkene **11** proceeded smoothly using 2 equivalents of 9-BBN-H in THF. Use of 3 equivalents of 9-BBN-H gave the intermediate borane, but the subsequent Suzuki coupling was inhibited. Oxidation of the crude reaction mixture in this case gave the expected alcohol **13**. Use of 2.2 equivalents of electrophile in the Suzuki reaction gave optimal results for the reaction; variations in the solvents and the temperature had a much smaller influence on the outcome of the reaction. The optimum conditions involved use of THF as solvent, with subsequent Suzuki reaction at room temperature (Table 1, entry 8). The stereochemical integrity of the hydroboration–Suzuki coupling sequence was confirmed by preparation of *ent*-**14a** from *ent*-**11** by the same procedure, followed by chiral phase HPLC analysis of **14a** and *ent*-**14a**.

Table 1 Optimisation studies for the Suzuki reaction

Entry	PhI (eq.)	Temperature	Solvent	Yield (%)[a]
1	1.1	rt	THF–DMF[b]	10
2	1.1	Δ	THF–DMF	25
3	2.2	rt	THF–DMF	57
4	3.3	rt	THF–DMF	25
5	2.2	Δ	THF–DMF	62
6	2.2	Δ	THF	56
7	2.2	Δ	THF–dioxane	37
8	2.2	rt	THF	64

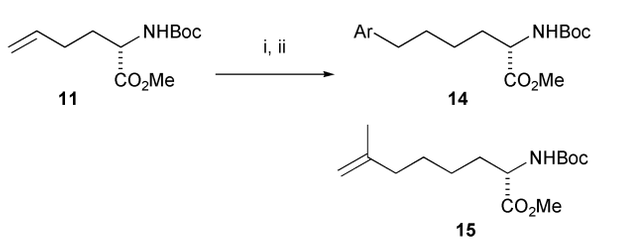
[a] Yields based on isolated product. [b] DMF was degassed prior to use.



11 **14a** **13**

Scheme 2 *Reagents and conditions:* (i) 9-BBN-H (2 eq.), THF (ii) PhI, $PdCl_2$(dppf) (5 mol%), K_3PO_4 (3 M), see Table 1 for solvents and conditions.

Having established the optimum conditions for the process, we applied them to generate a range of unnatural α-amino acids. The results of the coupling reactions are summarised in Table 2. Both electron-withdrawing and electron-donating substituted aromatic iodides were successful substrates giving the products **14b**–**14i** in good yield. An activated aryl bromide coupled successfully giving the product **14j** in 73%, a better result compared to the analogous aryl iodide (*cf* entries 9 and 10). 2-Bromopyridine also underwent efficient coupling to give the corresponding adduct **14k**. The expected selectivity for the iodide over the bromide was observed in the coupling with 2-bromoiodobenzene, giving the 2-bromophenyl derivative **14l**. Finally, the reaction with 2-bromopropene proceeded in good yield to give a homologated alkene **15** (Scheme 3).



11 **14** **15**

Scheme 3 *Reagents and conditions:* (i) 9-BBN-H (2 eq.), THF (ii) RX, $PdCl_2$(dppf) (5 mol%), K_3PO_4 (3 M), THF, rt, 16 h.

Microwave chemistry has become an important technique in palladium catalysed reactions.[12,13] Therefore, we repeated the Suzuki coupling with 2-bromo-1-iodobenzene using a microwave. With a reaction time of five minutes at 150 °C the corresponding product **14l** was obtained in a substantially improved 93% yield.

Table 2 Hydroboration–Suzuki cross coupling reactions

RX	R	Product	Yield (%)[a]
PhI	Ph	**14a**	64
2-O_2N–C_6H_4I	2-O_2N–C_6H_4	**14b**	78
3-O_2N–C_6H_4I	3-O_2N–C_6H_4	**14c**	27
4-O_2N–C_6H_4I	4-O_2N–C_6H_4	**14d**	66
4-MeO–C_6H_4I	4-MeO–C_6H_4	**14e**	52
2-$CH_3C_6H_4I$	2-$CH_3C_6H_4$	**14f**	26
4-$CH_3C_6H_4I$	4-$CH_3C_6H_4$	**14g**	75
1-Naphthyl-I	1-Naphthyl	**14h**	62
4-$MeO_2CC_6H_4I$	4-$MeO_2CC_6H_4$	**14i**	35
4-$EtO_2CC_6H_4Br$	4-$EtO_2CC_6H_4$	**14j**	73
2-BrPyridine	2-Pyridyl	**14k**	57
2-Br-1-IC_6H_4	2-BrC_6H_4	**14l**	38(93)[b]
CH_2=$CBrCH_3$	CH_2=CCH_3	**15**	50

[a] Yields based on isolated product. [b] Yield obtained using microwave irradiation.

Conclusions

We have extended the hydroboration–Suzuki coupling methodology to higher homologues of phenylalanine, using a combination of our copper-catalysed allylation chemistry with the hydroboration–Suzuki chemistry developed in other groups. We have also presented a preliminary result which indicates that microwave irradiation may substantially enhance the yields in these types of reaction.

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 sodium benzophenone ketyl. Petroleum ether refers to the fraction with a boiling point between 40–60 °C. Specific rotations were measured on a Perkin Elmer 241 automatic polarimeter at 589 nm (Na D-line) with a path length of 1 dm at the stated temperature. Concentrations are quoted in g per 100 mL and optical rotations are given in units of 10^{-1} deg cm^2g^{-1}. IR spectra were recorded on a Perkin Elmer Paragon 100 FTIR spectrophotometer (ν_{max} in cm^{-1}) at the University of Sheffield as thin films. Mass spectra were recorded in EI mode using a ProSpec magnetic sector instrument, or in ES-TOF mode using a Micromass LCT instrument. Nuclear magnetic resonance (NMR) spectra were recorded at the field strength in $CDCl_3$, using standard pulse sequences on a Bruker AC 250 or Bruker AC 400. Elemental analysis were carried out by the University of Sheffield Microanalysis Service. Unless otherwise specified, all the reagents used were purchased from commercial sources or prepared according to standard literature methods using references given in the text and purified as necessary prior to use by standard literature procedures. Organic extracts were dried over $MgSO_4$ and the solvent removed on a rotary evaporator under reduced pessure. The microwave reaction was carried out in a SmithCreator 300W focused microwave.

Methyl 2(*S*)-[*N*-(*tert*-butoxycarbonyl)amino]hex-5-enoate 11

Zinc dust (1.96 g, 30 mmol, Lancaster) was weighed into a 25 mL round bottom flask with a side arm and fitted with a 3-way tap. Iodine (76 mg) was added and the flask was heated with a heat gun under vacuum for ten minutes and the flask was flushed with nitrogen and evacuated and flushed a further three times. *N*-(*tert*-Butoxycarbonyl)-3-iodo-L-alanine methyl ester **12** (3.29 g, 10 mmol) dissolved in dry DMF (6.5 mL) 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 to room temperature and stirred for 1 hour to give the organozinc reagent **1**. The insertion process was monitored by TLC analysis (petroleum ethereum ether–ethyl acetate; 2 : 1). Whilst the zinc insertion reaction was in progress, CuBr·DMS (267 mg, 1.3 mmol) was weighed into a 25 mL 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 white powder to a light green powder. Dry DMF (6.5 mL) was then added followed by addition of allyl chloride (994 mg, 13 mmol). The reaction mixture was then cooled to −15 °C. Once the zinc insertion was judged to have reached completion (TLC) stirring of the reaction mixture was then stopped to allow the zinc powder to settle and the supernatant was removed *via* syringe (care being taken to minimise the transfer of zinc) 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 (265 mL) was added and stirring was continued for a further 15 minutes. The reaction mixture was transferred to a separating funnel and a further aliquot of ethyl acetate (400 mL) was added. The organic phase was washed successively with 1 M $Na_2S_2O_3$ (265 mL), water (2 × 265 mL), brine (530 mL) and dried. The solvent was removed to afford the product **11** (1.46 g, 60%), which exhibited an identical ^{1}H NMR spectrum to that in the literature. An analogous reaction using *ent*-**12** gave *ent*-**11**.

General procedure for hydroboration–Suzuki coupling

To the alkene **11** (1 eq.) in THF (1 mL per 0.2 mmol alkene) at 0 °C under nitrogen was added 9-BBN (0.5 M in THF, 2 eq.). The mixture was warmed to room temp. and stirred for 2 h. The flask was covered with foil and K_3PO_4 (3 M in H_2O, 2 eq.) was added carefully (H_2 evolution) followed quickly by addition of the aromatic halide (2.2 eq.) and $PdCl_2$(dppf) (5 mol%). The reaction mixture was stirred overnight, partitioned between diethyl ether and saturated aqueous sodium bicarbonate and the layers were separated. The aqueous layer was re-extracted with diethyl ether and the combined organic layers were dried, filtered and the solvent removed to give the crude product which was purified by flash column chromatography eluting with petroleum ether–ethyl acetate mixtures to afford the Suzuki coupling product. In all cases, the product was accompanied by a 9-BBN derived impurity which could be removed by the following procedure developed by Taylor:[8] the crude reaction product was dissolved in THF (3 mL per 0.2 mmol alkene) and aq. NaOH (1 M, 1 mL per 0.2 mmol alkene) was added followed by aq. H_2O_2 (30% w/v, 0.1 mL per 0.2 mmol alkene) and the mixture was stirred vigorously for 10 minutes at 0 °C. The reaction was diluted with diethyl ether and saturated aqueous $NaHCO_3$ and the layers were separated. The aqueous layer was re-extracted with diethyl ether and the combined layers were dried, filtered and concentrated under reduced pressure. In the case of the 2-pyridyl derivative **14k**, the oxidation procedure was omitted since the product could be obtained pure by direct chromatography of the crude product. In some cases the alcohol **13** was isolated as a by-product, indicating an incomplete Suzuki reaction.

Methyl (2*S*)-2-[(*tert*-butoxycarbonyl)amino]-6-hydroxy-hexanoate 13

The title compound **13** was isolated as an oil. Found: MH^+ 262.1648. $C_{12}H_{22}NO_5$ requires MH 262.1654; $\nu_{max.}$(film)/cm^{-1} 3612 (w), 3436 (w), 2981 (m), 2936 (m), 1741 (s), 1713 (s), 1503 (s) and 1368 (m); δ_H 1.42 (9H, s), 1.46–1.90 (6H, m), 3.63 (2H, t, *J* 6.5), 3.72 (3H, s), 4.23–4.35 (1H, m), 5.06 (1H, d, *J* 8.0); δ_C 21.6 (CH_2), 28.3 (3 × CH_3), 32.0 (CH_2), 32.5 (CH_2), 52.3 (CH_3), 53.3 (CH), 62.3 (CH_2), 79.9 (C), 155.5 (C), 173.4 (C); *m*/*z* 262 (MH^+); $[\alpha]_D^{17}$ +6.2 (*c* = 1.6 in CH_2Cl_2).

Methyl (2*S*)-2-[(*tert*-butoxycarbonyl)amino]-6-(phenyl)-hexanoate 14a

The title compound was prepared according to the general hydroboration–Suzuki coupling procedure outlined above by reaction with iodobenzene (0.05 mL). Purification by column chromatography eluting with a petroleum ether–ethyl acetate gradient afforded **14a** (123 mg, 64%) as an oil. Found: MH^+ 321.1947. $C_{18}H_{27}NO_4$ requires MH, 321.1940; $\nu_{max.}$(film)/cm^{-1} 3438 (w), 2935 (w), 1742 (s), 1713 (s), 1499 (s), 1454 (w), 1368 (m), 1213 (w) and 1165 (s); δ_H 0.99–1.58 (6H, m), 1.14 (9H, s), 2.3 (2H, t, *J* 8), 3.41 (3H, s), 3.94–4.05 (1H, m), 4.69 (1H, d, *J* 8), 6.81–7.01 (5H, m); δ_C 24.9 (CH_2), 28.3 (3 × CH_3), 30.9 (CH_2), 32.6 (CH_2), 36.6 (CH_2), 52.2 (CH_3), 53.4 (CH), 79.9 (C), 125.7 (CH), 128.3 (CH), 128.4 (CH), 142.2 (C), 155.4 (C), 173.4 (C); *m*/*z* 322 (MH^+); $[\alpha]_D^{17}$ +11 (*c* = 1.1 in CH_2Cl_2).

Methyl (2*R*)-2-[(*tert*-butoxycarbonyl)amino]-6-phenyl-hexanoate *ent*-14a

This compound was prepared in an identical fashion, but using *ent*-**11** as the starting material. $[\alpha]_D^{17}$ −11 (*c* = 1.15 in CH_2Cl_2). Chiral phase HPLC analysis of compounds **14a** and *ent*-**14a** using a Chiralpak AD column, a mobile phase of 5% EtOH–heptane with a flow rate of 1.0 mL min^{-1}, detection at a wavelength 215 nm, indicated an enantiomeric excess of 99%. R_t(*S*) 7.4 min, R_t(*R*) 10.1 min.

Methyl (2*S*)-2-[(*tert*-butoxycarbonyl)amino]-6-(2-nitrophenyl)-hexanoate 14b

The title compound was prepared according to the general hydroboration–Suzuki coupling procedure outlined above by reaction with 1-iodo-2-nitrobenzene (224 mg). Purification by column chromatography eluting with a petroleum ether–ethyl acetate gradient afforded **14b** (104 mg, 78%) as an oil. Found: MH^+ 367.1880. $C_{18}H_{27}N_2O_6$ requires MH, 367.1869; $\nu_{max.}$(film)/cm^{-1} 3690 (m), 3060 (s), 2986 (m), 2306 (m), 1742 (m), 1714 (m), 1606 (m), 1421 (s) and 1324 (s); δ_H 1.38 (9H, s), 1.40–1.68 (6H, m), 2.81 (2H, t, *J* 8), 3.68 (3H, s), 4.17–4.32 (1H, m), 4.95 (1H, d, *J* 8), 7.22–7.32 (2H, m), 7.41–7.49 (1H, m), 7.82 (1H, d, *J* 8); δ_C 25.3 (CH_2), 28.3 (3 × CH_3), 30.2 (CH_2), 32.5 (CH_2), 32.8 (CH_2), 52.3 (CH_3), 53.3 (CH), 80.0 (C), 124.7 (CH), 127.0 (CH), 131.9 (CH), 132.9 (CH), 137.1 (C), 149.3 (C), 155.5 (C), 173.3 (C); *m*/*z* 367 (MH^+), 389 (MNa^+), 405 (MK^+); $[\alpha]_D^{17}$ +7.7 (*c* = 1.3 in CH_2Cl_2).

Methyl (2*S*)-2-[(*tert*-butoxycarbonyl)amino]-6-(3-nitrophenyl)-hexanoate 14c

The title compound was prepared according to the general hydroboration–Suzuki coupling procedure outlined above by reaction with 1-iodo-3-nitrobenzene (110 mg). Purification by column chromatography eluting with a petroleum ether–ethyl acetate gradient afforded **14c** (20 mg, 27%) as an oil. Found: MH^+ 367.1884. $C_{18}H_{27}N_2O_6$ requires MH, 367.1869; $\nu_{max.}$(film)/cm^{-1} 3689 (s), 3600 (m), 3061 (s), 2305 (m), 1741 (m), 1715 (s), 1606 (s) and 1530 (s); δ_H 1.42 (9H, s), 1.56–1.90 (6H, m), 2.70 (2H, t, *J* 8.), 3.71 (3H, s), 4.24–4.34 (1H, m), 5.01 (1H, d, *J* 8.5), 7.37–7.51 (2H, m), 7.99–8.06 (2H, m); δ_C 24.8 (CH_2), 28.3 (3 × CH_3), 30.5 (CH_2), 32.6 (CH_2), 35.3 (CH_2), 52.3 (CH_3), 53.2 (CH), 79.9 (C), 121.1 (CH), 123.2 (CH), 129.2 (CH), 134.7 (CH), 144.1 (C), 148.3 (C), 155.5 (C), 173.3 (C); *m*/*z* 367 (MH^+), 389 (MNa^+), 405 (MK^+); $[\alpha]_D^{17}$ +20.0 (*c* = 0.5 in CH_2Cl_2).

Methyl (2*S*)-2-[(*tert*-butoxycarbonyl)amino]-6-(4-nitrophenyl)-hexanoate 14d

The title compound was prepared according to the general hydroboration–Suzuki coupling procedure outlined above by

reaction with 1-iodo-4-nitrobenzene (224 mg). Purification by column chromatography eluting with a petroleum ether–ethyl acetate gradient afforded **14d** (88 mg, 66%) as an oil. Found: MH^+ 367.1862. $C_{18}H_{27}N_2O_6$ requires MH, 367.1869; $\nu_{max.}$(film)/cm^{-1} 3435 (w), 2935 (w), 2306 (w), 1742 (m), 1713 (s), 1606 (w), 1520 (s) and 1348 (s); δ_H 0.97–1.61 (6H, m), 1.11 (9H, s), 2.39 (2H, t, *J* 8), 3.41 (3H, s), 3.92–4.04 (1H, m), 4.72 (1H, d, *J* 8), 6.99 (2H, d, *J* 8.5), 7.81 (2H, d, *J* 8.5); δ_C 24.8 (CH_2), 28.3 (3 × CH_3), 30.4 (CH_2), 32.5 (CH_2), 35.5 (CH_2), 52.3 (CH_3), 53.2 (CH), 79.9 (C), 123.6 (CH), 129.1 (CH), 146.3 (C), 150.1 (C), 155.3 (C), 173.2 (C); *m*/*z* 367 (MH^+); $[a]_D^{17}$ +11.1 (*c* = 0.9 in CH_2Cl_2).

Methyl (2*S*)-2-[(*tert*-butoxycarbonyl)amino]-6-(4-methoxyphenyl)hexanoate 14e

The title compound was prepared according to the general hydroboration–Suzuki coupling procedure outlined above by reaction with 4-iodoanisole (211 mg). Purification by column chromatography eluting with a petroleum ether–ethyl acetate gradient afforded **14e** (75 mg, 52%) as an oil. Found: MH^+ 352.2118. $C_{19}H_{30}NO_5$ requires MH, 352.2124; $\nu_{max.}$(film)/cm^{-1} 2934 (w), 1742 (m), 1713 (s), 1512 (s), 1368 (w), 1246 (m) and 1165 (m); δ_H 1.27–1.86 (6H, m), 1.43 (9H, s), 2.53 (2H, t, *J* 7.5), 3.41 (3H, s), 3.77 (3H, s), 4.22–4.33 (1H, m), 5.00 (1H, d, *J* 8), 6.80 (2H, d, *J* 8.5), 7.06 (2H, d, *J* 8.5); δ_C 24.8 (CH_2), 28.3 (3 × CH_3), 31.2 (CH_2), 32.6 (CH_2), 34.7 (CH_2), 52.2 (CH_3), 53.4 (CH), 55.3 (CH_3), 79.8 (C), 113.7 (CH), 129.2 (CH), 134.3 (C), 155.3 (C), 157.7 (C), 173.4 (C); *m*/*z* 352 (MH^+), 374 (MNa^+); $[a]_D^{17}$ +12.1 (*c* = 1.65 in CH_2Cl_2).

Methyl (2*S*)-2-[(*tert*-butoxycarbonyl)amino]-6-(2-methylphenyl)hexanoate 14f

The title compound was prepared according to the general hydroboration–Suzuki coupling procedure outlined above by reaction with 1-iodo-2-methylbenzene (0.11 mL). Purification by column chromatography eluting with a petroleum ether–ethyl acetate gradient afforded **14f** (35 mg, 26 %) as an oil. Found: MH^+ 335.2099. $C_{19}H_{30}NO_5$ requires MH, 335.2096; $\nu_{max.}$(film)/cm^{-1} 3430 (w), 2980 (m), 2936 (m), 1742 (s), 1713 (s), 1501 (s), 1365 (s) and 1165 (s); δ_H 1.38 (9H, s), 1.42–1.82 (6H, m), 2.22 (3H, s), 2.52 (2H, t, *J* 8), 3.66 (3H, s), 4.19–4.30 (1H, m), 4.94 (1H, d, *J* 8), 6.98–7.10 (4H, m); δ_C 19.3 (CH_3), 25.3 (CH_2), 28.3 (3 × CH_3), 29.7 (CH_2), 32.8 (CH_2), 33 (CH_2), 52.2 (CH_3), 53.4 (CH), 7 9.9 (C), 125.9 (CH),128.8 (CH), 130.2 (CH), 135.8 (C), 140.4 (C), 155.4 (C), 173.4 (C); *m*/*z* 335 (MH^+); $[a]_D^{17}$ +22.2 (*c* = 0.45 in CH_2Cl_2).

Methyl (2*S*)-2-[(*tert*-butoxycarbonyl)amino]-6-(4-methylphenyl)hexanoate 14g

The title compound was prepared according to the general hydroboration–Suzuki coupling procedure outlined above by reaction with 1-iodo-4-methylbenzene (196 mg). Purification by column chromatography eluting with a petroleum ether–ethyl acetate gradient afforded **14g** (101 mg, 75%) as an oil. Found: MH^+ 335.2088. $C_{19}H_{30}NO_5$ requires MH, 335.2096; $\nu_{max.}$(film)/cm^{-1} 3437 (w), 2981 (m), 2934 (m), 1742 (s), 1713 (s), 1502 (s) and 1165 (s); δ_H 1.29–1.87 (6H, m), 1.43 (9H, s), 2.30 (3H, s), 2.55 (2H, t, *J* 7.5), 3.71 (3H, s), 4.23–4.34 (1H, m), 4.98 (1H, d, *J* 8), 7.00–7.10 (4H, m); δ_C 20.9 (CH_3), 24.8 (CH_2), 28.3 (3 × CH_3), 31.1 (CH_2), 32.6 (CH_2), 35.1 (CH_2), 52.2 (CH_3), 53.4 (CH), 79.8 (C), 128.2 (CH), 128.9 (CH), 135.1 (C), 139.1 (C), 155.3 (C), 173.4 (C); *m*/*z* 335 (MH^+); $[a]_D^{17}$ +7.4 (*c* = 1.4 in CH_2Cl_2).

Methyl (2*S*)-2-[(*tert*-butoxycarbonyl)amino]-6-(1-naphthyl)-hexanoate 14h

The title compound was prepared according to the general hydroboration–Suzuki coupling procedure outlined above by reaction with 1-iodonaphthalene (0.13 mL). Purification by column chromatography eluting with a petroleum ether–ethyl acetate gradient afforded **14h** (92 mg, 62%) as an oil. Found: MH^+ 371.2097 $C_{12}H_{29}NO_4$ requires MH, 371.2096; $\nu_{max.}$(film)/cm^{-1} 3437 (w), 3063 (w), 2981 (m), 2939 (m), 2865 (w), 1742 (s), 1713 (s), 1596 (w) and 1502 (s); δ_H 1.38 (9H, s), 1.41–1.83 (6H, m), 3.0 (2H, t, *J* 7.5), 3.65 (3H, s), 4.20–4.31 (1H, m), 4.94 (1H, d, *J* 7), 7.20–7.48 (4H, m), 7.61–7.67 (1H, m), 7.75–7.80 (1H, m), 7.90–7.99 (1H, m); δ_C 25.43 (CH_2), 28.3 (3 × CH_3), 30.3 (CH_2), 32.7 (CH_2), 32.8 (CH_2), 52.2 (CH_3), 53.4 (CH), 79.9 (C), 123.8 (CH), 125.4 (CH), 125.5 (CH), 125.7 (CH), 125.95 (CH), 126.6 (CH), 128.8 (CH), 131.8 (CH), 133.9 (C), 138.3 (C), 155.4 (C), 173.4 (C); *m*/*z* 371 (MH^+); $[a]_D^{17}$ +11.4 (*c* = 1.75 in CH_2Cl_2) .

Methyl 4-{(5*S*)-5-[(*tert*-butoxycarbonyl)amino]-6-methoxy-6-oxohexyl}benzoate 14i

The title compound was prepared according to the general hydroboration–Suzuki coupling procedure outlined above by reaction with methyl 4-iodobenzoate (236 mg). Purification by column chromatography eluting with a petroleum ether–ethyl acetate gradient afforded **14i** (53 mg, 35 %) as an oil. Found: MH^+ 380.2068. $C_{20}H_{30}NO_6$ requires MH, 380.2073; $\nu_{max.}$(film)/cm^{-1} 3437 (w), 2953 (w), 1741 (s), 1716 (s), 1610 (w), 1502 (m), 1284 (s) and 1164 (s); δ_H 1.37 (9H, s), 1.48–1.83 (6H, m), 2.59 (2H, t, *J* 8), 3.65 (3H, s), 3.83 (3H, s), 4.16–4.30 (1H, m), 4.93 (2H, d, *J* 7.5), 7.16 (2H, d, *J* 8), 7.88 (2H, d, *J* 8); δ_C 24.8 (CH_2), 28.3 (3 × CH_3), 30.5 (CH_2), 32.6 (CH_2), 35.6 (CH_2), 51.9 (CH_3), 52.2 (CH), 53.2 (CH_3), 79.9 (C), 127.8 (C), 128.4 (CH), 129.7 (CH), 147.7 (C), 155.3 (C), 167.1 (C), 173.3 (C); *m*/*z* 380 (MH^+); $[a]_D^{17}$ +11.8 (*c* = 0.85 in CH_2Cl_2).

Ethyl 4-{(5*S*)-5-[(*tert*-butoxycarbonyl)amino]-6-(6-methoxy-6-oxohexyl}benzoate 14j

The title compound was prepared according to the general hydroboration–Suzuki coupling procedure outlined above by reaction with ethyl 4-bromobenzoate (0.15 mL). Purification by column chromatography eluting with a petroleum ether–ethyl acetate gradient afforded **14j** (115 mg, 73%) as an oil. Found: MH^+ 394.2238. $C_{21}H_{32}NO_6$ requires MH, 394.2230; $\nu_{max.}$(film)/cm^{-1} 3437 (w), 2983 (m), 2938 (m), 2863 (w), 1741 (s), 1712 (s), 1610 (m), 1502 (s), 1368 (s), 1283 (s), 1165 (s) and 1109 (s); δ_H 1.37 (3H, t, *J* 7), 1.42 (9H, s), 1.47–1.88 (6H, m), 2.64 (2H, t, *J* 7.5), 3.70 (3H, s), 4.22–4.40 (1H, m), 4.34 (2H, q, *J* 7), 4.99 (1H, d, *J* 8), 7.20 (2H, d, *J* 8), 7.93 (2H, d, *J* 8); δ_C 14.3 (CH_3), 24.8 (CH_2), 28.3 (3 × CH_3), 30.6 (CH_2), 32.6 (CH_2), 35.6 (CH_2), 52.2 (CH_3), 53.3 (CH), 60.8 (CH_2), 79.9 (C), 128.1 (C), 128.4 (CH), 129.6 (CH), 147.6 (C), 155.3 (C), 166.6 (C), 173.3 (C); *m*/*z* 394 (MH^+), 416 (MNa^+) $[a]_D^{17}$ +7.4 (*c* = 1.35 in CH_2Cl_2).

Methyl (2*S*)-2-[(*tert*-butoxycarbonyl)amino]-6-(2-pyridinyl)-hexanoate 14k

The title compound was prepared according to the general hydroboration–Suzuki coupling procedure outlined above by reaction with 2-bromopyridine (0.08 mL). Purification by column chromatography eluting with a petroleum ether–ethyl acetate gradient afforded **14k** (73 mg, 57%) as an oil. Found: MH^+ 322.1905. $C_{17}H_{26}N_2O_4$ requires MH, 322.1892; $\nu_{max.}$(film)/cm^{-1} 3436 (w), 2954 (w), 1743 (m), 1713 (s), 1502 (m), 1268 (s) and 1165 (s); δ_H 1.42 (9H, s), 1.55–1.91 (6H, m), 2.77 (2H, t, *J* 7.5), 3.71(3H, s), 4.22–4.33 (1H, m), 5.07 (1H, d, *J* 8), 7.05–7.15 (2H, m), 7.57 (1H, td, *J* 7.5, 1.5), 8.51 (1H, d, *J* 4.5); δ_C 24.9 (CH_2), 28.3 (3 × CH_3), 29.3 (CH_2), 32.4 (CH_2), 37.9 (CH_2), 52.2 (CH_3), 53.3 (CH), 79.8 (C), 121.0 (CH), 122.7 (CH), 136.3 (CH), 149.2 (CH, 155.4 (C), 161.8 (C), 173.4 (C); *m*/*z* 323 (MH^+); $[a]_D^{17}$ +7.4 (*c* = 1.35 in CH_2Cl_2).

Methyl (2*S*)-2-[(*tert*-butoxycarbonyl)amino]-6-(2-bromophenyl)-hexanoate 14l

The title compound was prepared according to the general hydroboration–Suzuki coupling procedure outlined above by reaction with 1-bromo-2-iodobenzene (0.11 mL). Purification by column chromatography eluting with a petroleum ether–ethyl acetate gradient afforded **14l** (56 mg, 38%) as an oil. Found: MH^+ 400.1143. $C_{18}H_{27}NO_4Br$ requires MH, 400.1123; $\nu_{max.}$(film)/cm^{-1} 3437 (w), 2982 (w), 2932 (m), 1742 (s), 1714 (s), 1502 (s), 1368 (m) and 1165 (s); δ_H 1.38 (9H, s), 1.48–1.88 (6H, m), 2.65 (2H, t, *J* 8), 3.67 (3H, s), 4.18–4.32 (1H, m), 4.94 (1H, d, *J* 8), 6.93–7.05 (1H, m), 7.10–7.18 (2H, m), 7.46 (1H, d, *J 8*); δ_C 25.0 (CH_2), 28.3 (CH_3), 29.4 (CH_2), 32.6 (CH_2), 35.9 (CH_2), 79.9 (CH_3), 124.4 (CH), 127.4 (CH), 127.5 (CH), 130.3 (CH), 132.8 (C), 141.5 (C), 155.4 (C), 173.4 (C); *m*/*z* 400 (MH^+), 422 (MNa^+); $[\alpha]_D^{17}$ +7.4 (*c* = 1.35 in CH_2Cl_2).

Methyl (2*S*)-2-[(*tert*-butoxycarbonyl)amino]-7-methyl-7-octenoate 15

The title compound was prepared according to the general hydroboration–Suzuki coupling procedure outlined above by reaction with 2-bromopropene (0.08 mL). Purification by column chromatography eluting with a petroleum ether–ethyl acetate gradient afforded **15** (58 mg, 50 %) as an oil. Found: MH^+ 286.2016. $C_{12}H_{29}NO_4$ requires MH, 286.2018; $\nu_{max.}$(film)/cm^{-1} 3684 (m), 3438 (w), 2936 (w), 1742 (s), 1713 (s), 1606 (m), 1502 (s) and 1165 (s); δ_H 1.24–1.85 (6H, m), 1.42 (9H, s), 1.67 (3H, s), 1.98 (2H, t, *J* 7), 3.71 (3H, s), 4.22–4.34 (1H, m), 4.60 (1H, br s), 4.70 (1H, br s), 5.00 (1H, d, *J* 7); δ_C 22.2 (CH_3), 24.8 (CH_2), 26.9 (CH_2), 28.2 (3 × CH_3), 32.4 (CH_2), 37.4 (CH_2), 52.1 (CH_3), 53.3 (CH), 79.7 (C), 109.9 (CH_2), 145.4 (C), 155.3 (C), 173.4 (C); *m*/*z* 286 (MH^+), 308 (MNa^+), 324 (MK^+); $[\alpha]_D^{17}$ +6.7 (*c* = 1.5 in CH_2Cl_2).

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