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Hydroboration–Suzuki cross coupling of unsaturated amino acids; the synthesis of pyrimine derivatives

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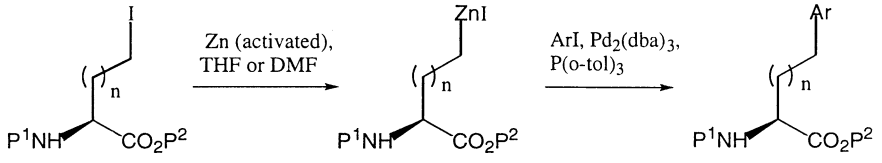
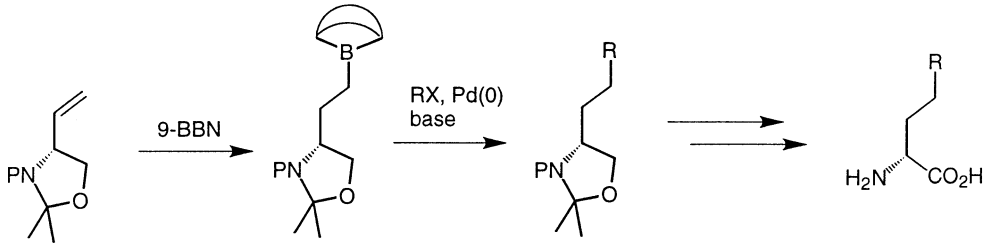
Abstract—Hydroboration of protected allylglycines with 9-BBN followed by Suzuki cross coupling of the resulting organoboranes proceeded smoothly giving a range of new bis-homophenylalanine and related derivatives in good yields (9 examples, 53–64%). One of the Suzuki coupling products has been elaborated to give the *N*-Cbz-protected natural product pyrimine. The hydroboration–Suzuki coupling of vinylglycine derivatives was also studied but was less efficient than with the allylglycine derivatives: the best results were obtained using disiamylborane·DMS as the hydroborating agent. © 2002 Published by Elsevier Science Ltd.

Non-proteinogenic α-amino acids are of value in terms of their biological importance and their utility as synthetic building blocks.[1,2] A number of preparative approaches to enantiopure, non-proteinogenic α-amino acids have been developed, many based on radical[3] and cationic[4] reagents ultimately derived from the chiral pool. However, the most popular approach in recent years has been to convert proteinogenic amino acids into alanine, homoalanine and bis-homoalanine anionic equivalents.[5] In this area, the organozinc approach of Jackson and co-workers is noteworthy.[6] They have prepared a family of organozinc reagents **1** which can be coupled with aryl iodides and related electrophiles under palladium-catalysed conditions to produce a range of phenylalanine, homo- and bis-homophenylalanine derivatives in good yields (Scheme 1).



1 (n = 0, 1, 2)
P^1 = Boc, Fmoc; P^2 = Me, Bn

Scheme 1.



2, P = Boc, Cbz

Scheme 2.

Keywords: hydroboration–Suzuki cross coupling; unsaturated amino acids; pyrimine derivatives.
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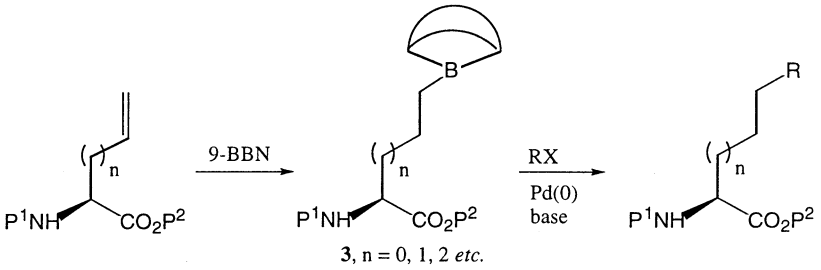


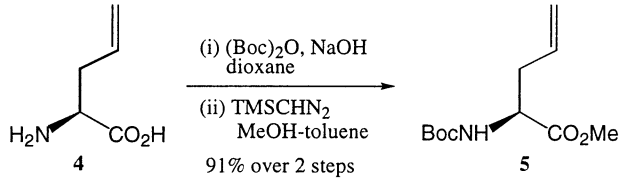
Scheme 3.

Recently, we described the synthesis of novel organoborane homoalanine anion equivalents **2**, which were simply and effectively transformed into a range of known and novel non-proteinogenic α-amino acids under mild conditions (Scheme 2).[7]

In extending the above methodology, we decided to investigate whether organoborane reagents **3** could be prepared directly by hydroboration of unsaturated amino acid derivatives (Scheme 3). Subsequent elaboration of the organoborane reagents **3** by Suzuki coupling would produce a range of novel non-proteinogenic amino acids in protected form. Such an approach, if successful, would avoid the need for the oxidation step required in Scheme 2, thereby minimising the risk of racemisation and extending the range of compatible halide partners in the Suzuki coupling process.[8] We felt that this methodology could complement the zinc chemistry in terms of ease of reagent preparation, tolerance in terms of reactions conditions and functional groups, etc. Preliminary results in this area have been published;[9] we now wish to report our investigations in full.

1. Hydroboration–Suzuki coupling studies of protected allylglycines

(L)-Allylglycine **4** is commercially available or can readily be prepared by literature methods.[10] *N*-Boc protection of amino acid **4** using $(Boc)_2O$/NaOH was followed by treatment with (trimethylsilyl)diazomethane giving *N*-Boc (L)-allylglycine methyl ester **5** {$[\alpha]_D$=+18.8 (*c* 1.0, $CHCl_3$); lit.[10c] +19.3 (*c* 1.5, $CHCl_3$)} in 91% overall yield as the key substrate for hydroboration–Suzuki coupling studies (Scheme 4).



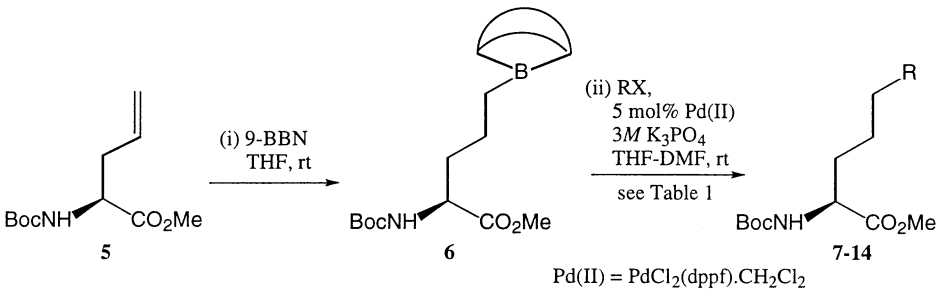
Scheme 4.

Danion et al. have recently described the hydroboration of protected allyl- and vinylglycine derivatives and other unsaturated amino acids as a route to ω-borono-α-amino acids some of which display interesting biological activities.[11] We first carried out the hydroboration of protected allylglycine **5** with 9-BBN (Scheme 5); 2 equiv. of the borane were required for the reaction to proceed to completion at room temperature. It seems likely that the first equivalent of 9-BBN reacts with, or is complexed by, the carbamate group. The triorganoborane adduct **6** was not isolated but was treated in situ with Suzuki coupling conditions. The same Suzuki coupling conditions as employed in our earlier studies[7,8] were adopted, i.e. $PdCl_2(dppf)\cdot CH_2Cl_2$/aq. K_3PO_4 in a solvent mixture of THF–DMF. The results of the couplings are summarised in Table 1.

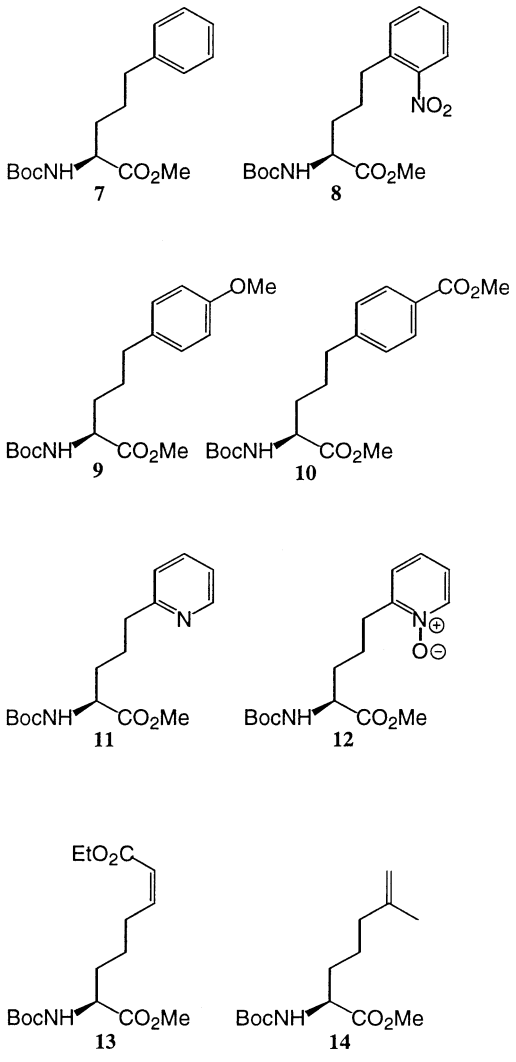
Table 1. Suzuki coupling of organoborane **6** with aryl and vinyl halides

Entry	RX	Product	Yield (%)
i	PhI	**7**	62
ii	2-NO_2–C_6H_4I	**8**	53
iii	4-MeO–C_6H_4I	**9**	60
iv	4-MeO_2C–C_6H_4Br	**10**	64
v	2-Br–py	**11**	62
vi	2-Br–py *N*-oxide·HBr	**12**	56
vii	(*Z*)-IHC=$CHCO_2Et$	**13**[a]	60
viii	CH_2=$CBrCH_3$	**14**	58

[a] Estimated NMR yield (**13** contaminated by an inseparable boron impurity).



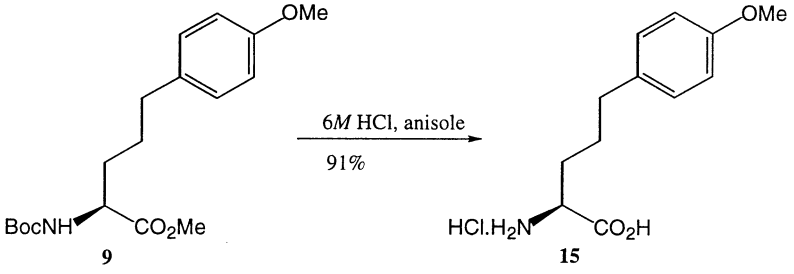
Scheme 5.



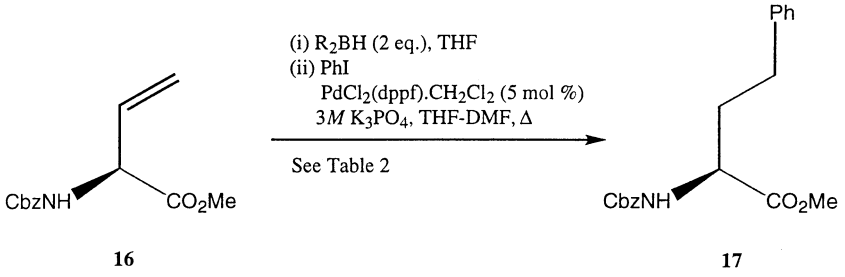
The first electrophile investigated in the Suzuki coupling process was iodobenzene (Table 1, entry i). We were delighted to observe efficient formation of the bis-homophenylalanine derivative **7** {$[\alpha]_D$=+21.3 (*c* 0.2, $CHCl_3$)} in 62% yield after stirring the reaction overnight at room temperature. Both electron withdrawing and electron donating aromatic bromides and iodides were found to be viable coupling partners successfully giving adducts **8–10** (Table 1, entries ii–iv). 2-Bromopyridine also underwent efficient transformation and the product **11** displayed spectroscopic data consistent with those previously reported for the racemic material (Table 1, entry v).[12] Likewise, Suzuki coupling of 2-bromopyridine *N*-oxide hydrobromide was accomplished to give **12** (Table 1, entry vi). Vinyl iodides and bromides also coupled smoothly. Ethyl *Z*-iodoacrylate gave adduct **13** with the *Z*-alkenyl stereochemistry present in the coupling partner being retained in the product **13** (Table 1, entry vii, *J*=11.6 Hz). 2-Bromopropene also coupled successfully giving **14** in 58% yield (Table 1, entry viii); in this example, 3 equiv. of 2-bromopropene were used due to its high volatility.

Polarimetry measurements confirmed that stereochemical integrity was conserved during the hydroboration–Suzuki coupling sequence. Hydrolysis of **9** with 6 M HCl at 70°C gave the known[13] amino acid product **15** which had an optical rotation consistent with that previously reported {$[\alpha]_D$=+31.2 (*c* 0.3, 5 M HCl–DMF, 1:1); lit.[13] (*ent*-**15**) −31.8 (*c* 2.0, 5 M HCl–DMF, 1:1)} (Scheme 6).

Other *N*-protected allylglycine derivatives were investigated to establish their compatibility with the hydroboration–Suzuki coupling sequence. *N*,*N*-DiBoc- and *N*-trityl-allylglycine methyl ester were prepared from commercially available allylglycine and subjected to 9-BBN hydroboration followed by Suzuki coupling with 2-nitro-iodobenzene. In both cases coupling proceeded to



Scheme 6.



Scheme 7.

give the *N*-protected analogue corresponding to adduct **8**. However, the overall yields were lower than with *N*-Boc protection (*N*-Boc, 53%; *N*,*N*-DiBoc, 45%; *N*-trityl 44%) and so the choice of the *N*-Boc derivative **5** for the hydroboration-coupling sequence seems appropriate.

2. Hydroboration–Suzuki coupling studies of protected vinylglycines

Having achieved encouraging results for the preparation of novel bis-homophenylalanine derivatives via the hydroboration–Suzuki coupling of protected allylglycine **5**, we next turned our attention to vinylglycine. In view of the commercial availability of *N*-Cbz vinylglycine methyl ester **16**, attention was focussed on its elaboration (Scheme 7 and Table 2). Initial attempts involved using iodobenzene and the same 9-BBN-Suzuki coupling conditions which were successful in the allylglycine studies. However, the starting alkene **16** required 5 molar equiv. of 9-BBN for complete consumption and none of the desired phenyl adduct **17** was obtained (entry i).[14] We therefore investigated the use of other dialkylboranes which are known[8a] to provide trialkylboranes suitable for Suzuki coupling (entries ii–v). The best result, a 32% yield for the formation of adduct **17**, was obtained using disiamylborane·SMe_2 as the hydroborating agent; the dimethyl sulfide (DMS) was removed in vacuo prior to Suzuki coupling otherwise catalyst poisoning occurred. The product **17** {$[\alpha]_D=+14.4$ (*c* 0.5, CH_2Cl_2); lit.[6c] $[\alpha]_D=+14.4$ (*c* 0.5, CH_2Cl_2)} was obtained in enantiomerically pure form.

Table 2. Hydroboration–Suzuki coupling of alkene **16**

Entry	R_2BH	Yield of **17** (%)
i	9-BBN (5 equiv.)	0
ii	Cy_2BH·THF	10
iii	Cy_2BH·DMS	11
iv	Sia_2BH·THF	22
v	Sia_2BH·DMS	32

In view of these disappointing results, no further studies were carried out in this area. It should be noted that homophenylalanine derivatives are available using the related chemistry shown in Scheme 2,[7] and this is our preferred route.

3. Application to the synthesis of pyrimine derivatives

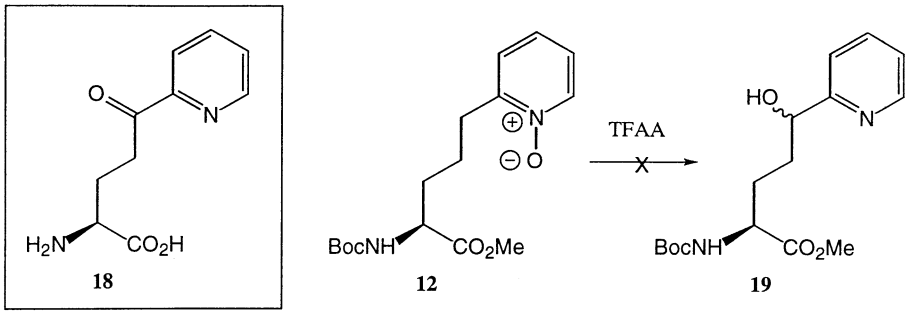
Finally, the utility of the bis-homophenylalanine equivalent **6** was demonstrated in the natural product arena by preparing derivatives of pyrimine **18**, an Fe(II)-binding agent isolated from a *Pseudomonas* species found in soil by Shiman et al. (Scheme 8).[15,16]

The availability of the *N*-oxide Suzuki adduct **12** led us to investigate the possibility of using the Boekelheide reaction[17,18] for oxidation at the benzylic position as required in the natural product. However, treatment of *N*-oxide **12** with trifluoroacetic acid anhydride (TFAA) under the improved conditions developed for the Boekelheide reaction by Balavoine et al.[18] resulted in decomposition of the starting material **12** and none of the expected product **19** was obtained (Scheme 8).

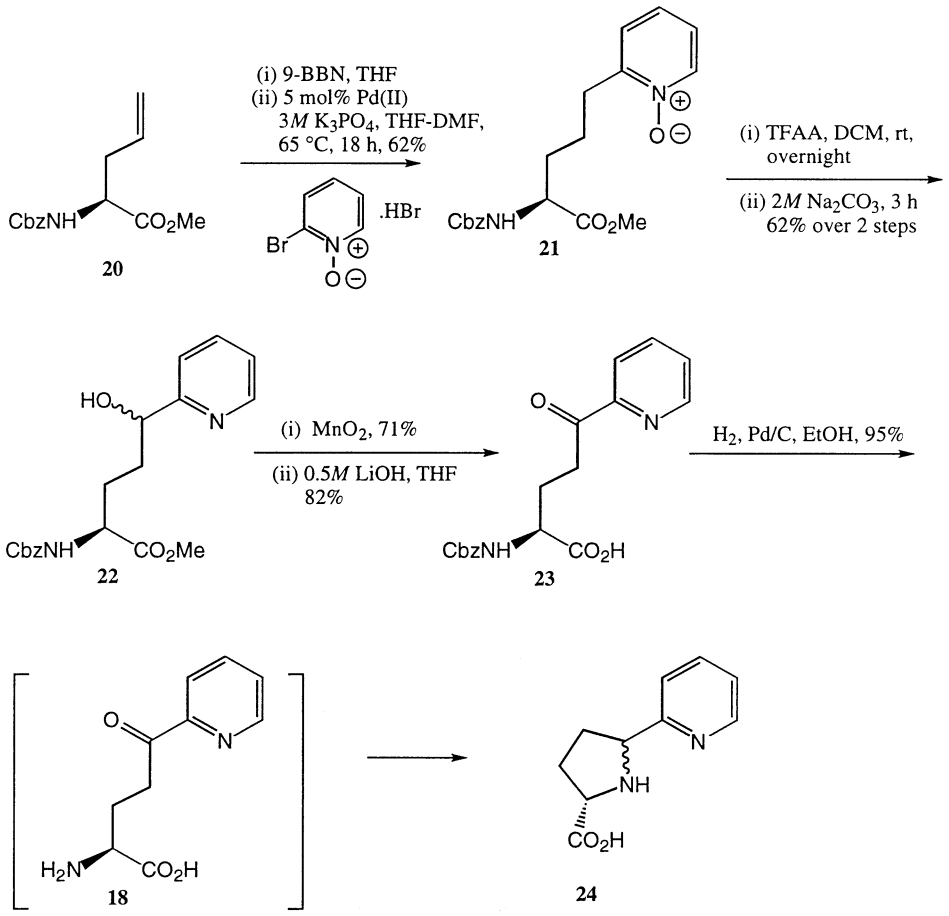
On the assumption that *N*-Boc protection is incompatible with the modified Boeklelheide reaction conditions, we followed the same approach but with the more robust *N*-Cbz protecting group (Scheme 9). Thus, treatment of the known allylglycine derivative **20**[19] with 9-BBN followed by Suzuki coupling with 2-bromopyridine *N*-oxide hydrobromide salt gave adduct **21**, as expected. Exposure of *N*-oxide **21** to TFAA gave the hoped-for Boekelheide reaction producing alcohol **22** as a mixture of diastereomers (approximately 1:1) in 62% yield after saponification of the intermediate trifluoroacetates.

Alcohol **22** was oxidised with manganese dioxide and then saponification using aqueous lithium hydroxide in THF gave *N*-Cbz-protected pyrimine **23**, which was fully characterised. Attempted synthesis of pyrimine **18** from *N*-Cbz pyrimine **23** by hydrogenolysis gave the unexpected amino acid product **24** (ca. 1:1 mixture of diastereoisomers) presumably arising from cyclisation of the intermediate amino ketone **18** and then non-selective imine reduction.[20]

In conclusion, a facile procedure for the synthesis of a range of new bis-homophenylalanine derivatives has been developed by the hydroboration–Suzuki coupling of protected allylglycines. Protected vinylglycine has also been employed in a similar sequence, although less successfully. We are currently developing a polymer-supported version of this methodology so as to allow a combinatorial approach to the synthesis of non-proteinogenic amino acids for use in medicinal chemistry.



Scheme 8.



Scheme 9.

4. Experimental

4.1. General

See Ref. 7c.

4.1.1. Methyl (2*S*)-2-[(*tert*-butoxycarbonyl)amino]-4-pentenoate (5). (i) A solution of L-2-amino-4-pentenoic acid **4** (1 g, 8.69 mmol) in 1 M NaOH (20 mL) and 1,4-dioxane (10 mL) at 0°C was treated with di-*tert*-butyl dicarbonate (2.28 g, 10.5 mmol) and the mixture allowed to warm to rt and the pH re-adjusted to 9 when required. The reaction was complete in 2 days by TLC. The dioxane was removed in vacuo and the mixture washed with Et_2O (20 mL) to remove any di-*tert*-butyl dicarbonate. The aqueous layer was acidified to pH 2 with 2 M H_2SO_4 and extracted with EtOAc (4×50 mL) saturating the aqueous layer with NaCl each time. The combined organic layers were dried, filtered and the solvent removed in vacuo to furnish the *N*-Boc protected amino acid (1.74 g, 93%) as a colourless oil which was used without further purification.

(ii) *N*-(*tert*-Butoxycarbonyl)-L-2-amino-4-pentenoic acid (1.47 g, 6.83 mmol) was dissolved in MeOH (13 mL) and toluene (13 mL) and (trimethylsilyl)diazomethane (2 M solution in hexanes, 6.84 mL, 13.7 mmol) added until there was a permanent change in colour (colourless to straw coloured). The reaction was left to stir for 30 min after which all volatile components were removed in vacuo. The residue was purified by column chromatography (light petroleum–EtOAc, 2:1) to yield the title compound **5** (1.54 g, 98%) as a colourless oil, R_f 0.39 (light petroleum–EtOAc, 3:1); $[\alpha]_D=+18.8$ (*c* 1.0, $CHCl_3$); lit.[10c] $[\alpha]_D=+19.3$ (*c* 1.5, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) δ 1.47 (9H, s), 2.42–2.61 (2H, m), 3.74 (3H, s), 4.34–4.44 (1H, m), 5.06 (1H, br s), 5.12 (2H, m), 5.72 (1H, m). The spectroscopic data were consistent with those reported.[10c]

4.2. General procedure for hydroboration–Suzuki coupling

To the alkene **5**, **16** or **20** (1 equiv.) in THF (1 mL per 0.2 mmol alkene) at 0°C under nitrogen was added 9-BBN (0.5 M in THF, 2 equiv.). The mixture was warmed to rt and stirred for 2 h. The flask was covered with foil and K_3PO_4 (3 M in H_2O, 2 equiv.) was added carefully (H_2 evolution) followed quickly by addition of the organic halide (ca. 1.1 equiv.) in dry degassed DMF (1 mL per 0.2 mmol alkene) and $PdCl_2(dppf)\cdot CH_2Cl_2$ (0.05 equiv.) under nitrogen. The reaction was stirred overnight and the solvent was removed in vacuo. The residue was taken up in Et_2O (25 mL per 0.2 mmol alkene) and saturated aq. $NaHCO_3$ (10 mL per 0.2 mmol alkene). The aqueous layer was re-extracted with Et_2O (25 mL per 0.2 mmol alkene) and the combined organic layers were dried, filtered and concentrated in vacuo to give the crude product which was purified by flash column chromatography eluting with light

petroleum–EtOAc mixtures to afford the Suzuki coupling product.

In some cases, the product was accompanied by a 9-BBN derived impurity which could be removed by the following procedure: 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 subsequently by aq. H_2O_2 (60% w/v, 0.2 mL per 0.2 mmol alkene) and the mixture was stirred vigorously for 10 min at 0°C. The reaction was diluted with Et_2O (20 mL per 0.2 mmol alkene) and saturated aq. $NaHCO_3$ (10 mL per 0.2 mmol alkene). The aqueous layer was re-extracted with Et_2O (25 mL per 0.2 mmol alkene) and the combined organic layers were dried, filtered and concentrated in vacuo prior to chromatography as above.

4.2.1. Methyl (2*S*)-2-[(*tert*-butoxycarbonyl)amino]-5-phenylpentanoate (7). The title compound **7** was prepared according to the general hydroboration–Suzuki coupling procedure outlined above by reaction with iodobenzene (124 mg, 0.61 mmol, 1.05 equiv.). Purification by column chromatography eluting with light petroleum–EtOAc (4:1) yielded **7** (110 mg, 62%) as a colourless oil, R_f 0.35 (light petroleum–EtOAc, 3:1); $[\alpha]_D=+21.3$ (*c* 0.2, $CHCl_3$); IR (film) 3369, 3025, 2977, 2864, 1745, 1715, 1603, 1518 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.44 (9H, s), 1.54–1.91 (4H, m), 2.55–2.70 (2H, m), 3.72 (3H, s), 4.28–4.42 (1H, m), 4.99 (1H, d, *J*=8.0 Hz) and 7.13–7.34 (5H, m); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 27.7, 28.9, 32.9, 35.9, 52.9, 53.9, 80.5, 126.5, 129.0 (×2), 142.3, 156.0, 174.0; CIMS *m*/*z* 325 (MNH_4^+, 1), 308 (MH^+, 7), 208 (100); HRCIMS Found: MH^+, 308.1857. $C_{17}H_{25}NO_4$ requires MH, 308.1862.

4.2.2. Methyl (2*S*)-2-[(*tert*-butoxycarbonyl)amino]-5-(2-nitrophenyl)pentanoate (8). The title compound **8** was prepared according to the general hydroboration–Suzuki coupling procedure outlined above by reaction with 1-iodo-2-nitrobenzene (140 mg, 0.56 mmol). Purification by column chromatography eluting with hexane–EtOAc (3:1) yielded **8** (95 mg, 53%) as a light yellow oil, R_f 0.24 (light petroleum–EtOAc, 2:1); $[\alpha]_D=+15.0$ (*c* 0.8, $CHCl_3$); IR (film) 3376, 2977, 2939, 2871, 1745, 1713, 1610, 1577, 1525, 1456, 1365 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.43 (9H, s), 1.62–1.98 (4H, m), 2.89 (2H, app t, *J*=8.0 Hz), 3.73 (3H, s), 4.27–4.42 (1H, m), 5.05 (1H, d, *J*=7.5 Hz), 7.31–7.36 (2H, m), 7.47–7.54 (1H, m), 7.88 (1H, d, *J*=7.0 Hz); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 27.0, 28.9, 33.1, 33.2, 53.0, 53.7, 80.6, 125.4, 127.8, 132.5, 133.6, 137.3, 149.9, 156.0, 173.8; CIMS *m*/*z* 370 (MNH_4^+, 13), 353 (MH^+, 3) and 253 (100); HRCIMS Found: MNH_4^+, 370.1979. $C_{17}H_{24}N_2O_6$ requires MNH_4, 370.1978.

4.2.3. Methyl (2*S*)-2-[(*tert*-butoxycarbonyl)amino]-5-(4-methoxyphenyl)pentanoate (9). The title compound **9** was prepared according to the general hydroboration–Suzuki coupling procedure outlined above by reaction with 4-methoxy-iodobenzene (77 mg, 0.33 mmol). Purification by column chromatography eluting with light petroleum–EtOAc (4:1) yielded **9** (61 mg, 60%) as a colourless oil, R_f 0.35 (light petroleum–EtOAc, 3:1); $[\alpha]_D=+17.5$ (*c* 0.8, $CHCl_3$); IR (film) 3362, 2977, 2936, 1744, 1716, 1610, 1520, 1365 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.43 (9H, s), 1.56–1.98 (4H, m), 2.51–2.62 (2H, m), 3.71 (3H, s), 3.77 (3H, s), 4.27–4.40 (1H, m), 5.03 (1H, br d, *J*=8.5 Hz), 6.81 (2H, d, *J*=8.5 Hz), 7.06 (2H, d, *J*=8.5 Hz); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 27.9, 28.9, 32.8, 35.0, 52.8, 53.9, 55.9, 80.5, 114.4, 129.9, 134.4, 156.0, 158.4, 174.0; CIMS *m*/*z* 355 (MNH_4^+, 7), 338 (MH^+, 8), 238 (100); HRCIMS Found: MH^+, 338.1962. $C_{18}H_{27}NO_5$ requires MH, 338.1967.

4.2.4. Methyl 4-{(4*S*)-4-[(*tert*-butoxycarbonyl)amino]-5-methoxy-5-oxopentyl}benzoate (10). The title compound **10** was prepared according to the general hydroboration–Suzuki coupling procedure outlined above by reaction with methyl 4-bromobenzoate (42 mg, 0.2 mmol). Purification by column chromatography eluting with light petroleum–EtOAc (3:1) yielded **10** (42 mg, 64%) as a colourless oil, R_f 0.27 (light petroleum–EtOAc, 3:1); $[\alpha]_D=+16.2$ (*c* 1.5, $CHCl_3$); IR (film) 3363, 2953, 2864, 1720, 1610, 1513, 1437, 1366, 1281 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.42 (9H, s), 1.55–1.91 (4H, m), 2.57–2.78 (2H, m), 3.71 (3H, s), 3.89 (3H, s), 4.25–4.41 (1H, m), 5.03 (1H, br d, *J*=8.0 Hz), 7.22 (2H, d, *J*=8.0 Hz), 7.94 (2H, d, *J*=8.0 Hz); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 26.7, 28.3, 32.2, 35.2, 51.9, 52.2, 53.0, 79.9, 127.9, 128.4, 129.7, 147.1, 155.3, 167.0, 173.2; CIMS *m*/*z* 383 (MNH_4^+, 4), 366 (MH^+, 1), 266 (100); HRCIMS Found: MNH_4^+, 383.2189. $C_{19}H_{27}NO_6$ requires MNH_4, 383.2182.

4.2.5. Methyl (2*S*)-2-[(*tert*-butoxycarbonyl)amino]-5-(2-pyridinyl)pentanoate (11). The title compound **11** was prepared according to the general hydroboration–Suzuki coupling procedure outlined above by reaction with 2-bromopyridine (34 mg, 0.22 mmol). Purification by column chromatography eluting with light petroleum–EtOAc (1:2) yielded **11** (38 mg, 62%) as a colourless oil, R_f 0.35 (EtOAc); $[\alpha]_D=+15.0$ (*c* 0.8, $CHCl_3$); IR (film) 3201, 2886, 2726, 1740, 1704, 1538, 1455, 1377 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.41 (9H, s), 1.58–1.92 (4H, m), 2.79 (2H, td, *J*=7.0, 2.5 Hz), 3.70 (3H, s), 4.21–4.40 (1H, m), 5.17 (1H, br s, *J*=7.5 Hz), 7.06–7.13 (2H, m), 7.57 (1H, td, *J*=7.5, 1.5 Hz), 7.50 (1H, d, *J*=4.5 Hz); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 25.3, 28.3, 32.1, 37.5, 52.2, 53.3, 79.7, 121.1, 122.8, 136.3, 149.2, 155.7, 161.2, 173.2; CIMS *m*/*z* 309 (MH^+, 100), 209 (46); HRCIMS Found: MH^+, 309.1810. $C_{16}H_{24}N_2O_4$ requires MH, 309.1814.

The spectroscopic data were consistent with those reported for the racemate.[12]

4.2.6. Methyl (2*S*)-2-[(*tert*-butoxycarbonyl)amino]-5-(1-oxido-2-pyridinyl)pentanoate (12). The title compound **12** was prepared according to the general hydroboration–Suzuki coupling procedure by reaction with 2-bromopyridine-*N*-oxide hydrobromide (56 mg, 0.22 mmol, 1.2 equiv.) in the presence of K_3PO_4 (3 M in H_2O, 0.2 mL, 0.59 mmol, 3.2 equiv.). In addition to the standard procedure the reaction was heated to 65°C overnight, then cooled and the solvent was removed in vacuo and purified directly by column chromatography eluting with EtOAc–EtOH (5:1) to afford **12** (33 mg, 56%) as a colourless oil, R_f 0.10 (EtOAc–EtOH, 10:1); $[\alpha]_D=+15.4$ (*c* 0.2, $CHCl_3$); IR (film) 3363, 2976, 2930, 1741, 1707, 1526, 1492, 1439,

1366 cm^{-1}; ^1H NMR (270 MHz, MeOH-d_4) δ 1.43 (9H, s), 1.60–1.93 (4H, m), 2.96 (2H, app t, J=6.0 Hz), 3.71 (3H, s), 4.15–4.20 (1H, m), 4.86–4.90 (1H, m), 7.37–7.47 (1H, m), 7.50–7.60 (2H, m), 8.33 (1H, d, J=6.5 Hz); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 22.1, 28.2, 30.0, 32.2, 52.3, 53.1, 79.8, 123.6, 125.5, 126.1, 139.7, 151.8, 155.4, 173.1; CIMS m/z 325 (MH^+, 65), 309 (MH−O, 100); HRCIMS Found: MH^+ 325.1763. $C_{16}H_{24}N_2O_5$ requires MH, 325.1763.

4.2.7. Methyl (2*S*,6*Z*)-2-[(*tert*-butoxycarbonyl)amino]-8-ethoxy-8-oxo-6-octenoate (13). The title compound **13** was prepared according to the general hydroboration–Suzuki coupling procedure outlined above by reaction with (*Z*)-3-iodoethylacrylate (40 mg, 0.18 mmol). Purification by column chromatography eluting with light petroleum–EtOAc (4:1) yielded **13** (56 mg, contaminated by a 9-BBN derived impurity, approx. yield 60%) as a colourless oil, R_f 0.28 (light petroleum–EtOAc, 3:1); ^1H NMR (270 MHz, $CDCl_3$) δ 1.27 (3H, t, J=7.5 Hz), 1.43 (9H, s), 1.50–1.90 (4H, m), 2.66 (2H, app q, J=7.5 Hz), 3.73 (3H, s), 4.15 (2H, q, J=7.5 Hz), 4.34–4.43 (1H, m), 5.00–5.21 (1H, app d, J=7.5 Hz), 5.77 (1H, dt, J=11.5, 2.0 Hz), 6.15 (1H, dt, J=11.5, 7.5 Hz); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 14.2, 24.7, 28.2, 28.3, 32.3, 52.2, 53.3, 59.8, 79.8, 120.3, 149.0, 155.3, 166.2, 173.3; CIMS m/z 347 (MNH_4^+, 2), 330 (MH^+, 9), 230 (100); HRCIMS Found: MH^+, 330.1923. $C_{16}H_{27}NO_6$ requires MH, 330.1917.

4.2.8. Methyl (2*S*)-2-[(*tert*-butoxycarbonyl)amino]-6-methyl-6-heptenoate (14). The title compound **14** was prepared according to the general hydroboration–Suzuki coupling procedure outlined above by reaction with 2-bromopropene (72 mg, 0.59 mmol, 3 equiv.). Purification by column chromatography eluting with light petroleum–EtOAc (3:1) yielded 14 (31 mg, 58%) as a colourless oil, R_f 0.31 (light petroleum–EtOAc, 4:1); $[\alpha]_D$=+13.1 (*c* 0.5, $CHCl_3$); IR (film) 3447, 3357, 2967, 2931, 2863, 1747, 1715, 1699, 1525, 1453, 1169 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.44 (9H, s), 1.40–1.90 (4H, m), 1.69 (3H, s), 2.02 (2H, t, J=7.5 Hz), 3.74 (3H, s), 4.27–4.42 (1H, m), 4.66 (1H, br s), 4.71 (1H, br s), 5.02 (1H, d, J=9.0 Hz); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 22.2, 23.1, 28.3, 32.2, 37.1, 52.2, 53.3, 79.9, 110.4, 145.0, 155.3, 173.4; CIMS m/z 289 (MNH_4^+, 11), 272 (MH^+, 45), 172 (100); HRCIMS Found: MH^+, 272.1859. $C_{14}H_{25}NO_4$ requires MH, 272.1862.

4.2.9. (2*S*)-2-Amino-5-(4-methoxyphenyl)pentanoic acid hydrochloride (15). A stirred solution of protected amino acid **9** (47 mg, 0.14 mmol) and anisole (31 mg, 0.29 mmol) in 6 M HCl was heated at 70°C for 6 h. The reaction was cooled and then diluted with H_2O (10 mL) and washed with EtOAc (2×10 mL) and the aqueous layer was concentrated in vacuo and azeotroped with toluene (3×5 mL) to give the title compound **15** (33 mg, 91%) as a colourless solid, mp 191–193°C; $[\alpha]_D$=+31.2 (*c* 0.3, 5 M HCl–DMF, 1:1); lit. (*ent*)[13] $[\alpha]_D$=−31.8 (*c* 2.0, 5 M HCl–DMF, 1:1); ^1H NMR (270 MHz, CF_3CO_2D) δ 2.11–2.33 (2H, m), 2.40–2.58 (2H, m), 3.00–3.12 (2H, m), 4.32 (3H, s), 4.71 (1H, t, J=6.5 Hz), 7.33 (2H, d, J=8.0 Hz), 7.50 (2H, d, J=8.0 Hz).

The spectroscopic data were consistent with those reported.[21] The melting point of this compound has not been reported before.

4.2.10. Methyl (2*S*)-2-{[(benzyloxy)carbonyl]amino}-4-phenylbutanoate (17). (a) *By hydroboration–Suzuki coupling of **16** with disiamylborane·DMS*. To alkene **16** (24 mg, 96 μmol) in THF (0.6 mL) at 0°C under nitrogen was added disiamylborane freshly prepared from BH_3·DMS[22] (1.2 M solution in THF, 0.16 mL, 0.19 mmol) and the reaction was warmed to rt and stirred for 1.5 h until TLC showed consumption of starting material. The solvent and DMS were removed in vacuo and the residue re-dissolved in THF (0.4 mL) and DMF (0.4 mL). K_3PO_4 (3 M in H_2O, 0.06 mL, 0.18 mmol) was added followed by quick addition of iodobenzene (21 mg, 0.10 mmol) and finally $PdCl_2(dppf)\cdot CH_2Cl_2$ (3 mg, 4 μ mol) under nitrogen. The reaction was heated to 70°C for 5 h and then cooled and the solvent was removed in vacuo. The residue was taken up in Et_2O (10 mL) and saturated aq. $NaHCO_3$ (10 mL). The aqueous layer was re-extracted with Et_2O (2×10 mL) and the combined organic layers were dried, filtered and concentrated in vacuo to give the crude product as a brown oil which was purified by column chromatography (light petroleum–EtOAc, 3:1) to afford the title compound **17** (10 mg, 32%) as a colourless oil, $[\alpha]_D$=+14.4 (*c* 0.5, CH_2Cl_2); lit.[6c] $[\alpha]_D$=+14.4 (*c* 0.5, CH_2Cl_2); ^1H NMR (270 MHz, $CDCl_3$) δ 1.95–2.07 (1H, m), 2.14–2.27 (1H, m), 2.69 (2H, app t, J=8.0 Hz), 3.72 (3H, s), 4.40–4.52 (1H, m), 5.15 (2H, s), 5.48 (1H, d, J=8.0 Hz), 7.12–7.50 (10H, m).

The spectroscopic data were consistent with those reported.[6c,7c]

(b) *By hydroboration–Suzuki coupling of **16** with dicyclohexylborane·DMS*. The title compound **17** was prepared using the same procedure as in (a) hydroboration of alkene **16** (20 mg, 80 μmol) was carried out with a 0.07 M solution of dicyclohexylborane·DMS.[22] The Suzuki coupling reaction was complete in 2 h at 50°C. The product (3 mg, 11%) displayed spectroscopic properties identical to those of compound **17**.

(c) *By hydroboration–Suzuki coupling of **16** with disiamylborane·THF*. The title compound **17** was prepared using the same procedure as in (a) hydroboration of alkene **16** (14 mg, 56 μmol) was carried out with a 0.83 M solution of disiamylborane·THF.[22] The Suzuki coupling reaction was complete in 2 h at 60°C. The product (4 mg, 22%) displayed spectroscopic properties identical to those of compound **17**.

(d) *By hydroboration–Suzuki coupling of **16** with dicyclohexylborane·THF*. The title compound **17** was prepared using the same procedure as in (a) hydroboration of alkene **16** (32 mg, 0.13 mmol) was carried out with a 1 M solution of dicyclohexylborane·THF.[22] The Suzuki coupling reaction was complete in 2 h at 50°C. The product (4 mg, 10%) displayed spectroscopic properties identical to those of compound **17**.

4.2.11. Methyl (2*S*)-2-{[(benzyloxy)carbonyl]amino}-5-(1-oxido-2-pyridinyl)pentanoate (21). Using alkene **20**, the title compound **21** was prepared according to the general

hydroboration–Suzuki coupling procedure by reaction with 2-bromopyridine *N*-oxide hydrobromide (184 mg, 0.72 mmol) in the presence of K_3PO_4 (3 M in H_2O, 0.7 mL, 2.1 mmol, 3.2 equiv.). In addition to the standard procedure the reaction was heated to 65°C overnight, then cooled and the solvent was removed in vacuo and purified directly by column chromatography eluting with EtOAc–EtOH (1:1) to afford **21** (145 mg, 62%) as a colourless oil, R_f 0.27 (EtOAc–EtOH, 1:1); $[\alpha]_D$=+12.5 (*c* 0.2, $CHCl_3$); IR (film) 3343, 3227, 3027, 2952, 1715, 1543, 1440 cm^{-1}; ^1H NMR (270 MHz, MeOH-d_4) δ 1.70–1.98 (4H, m), 2.89–3.00 (2H, m), 3.75 (3H, s), 4.40–4.49 (1H, m), 5.11 (2H, s), 5.48 (1H, d, *J*=8.0 Hz), 7.14–7.35 (8H, m), 8.30 (1H, d, *J*=6.0 Hz); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 22.1, 29.8, 31.7, 51.2, 53.6, 66.6, 123.5, 125.4, 126.1, 127.8, 128.0, 128.2, 136.1, 139.4, 151.4, 156.0, 172.7; CIMS *m/z* 359 (MH^+, 4) and 343 (MH−O, 100); HRCIMS Found: MH^+ 359.1607. $C_{19}H_{22}N_2O_5$ requires MH, 359.1607.

4.2.12. Methyl (2*S*)-2-{[(benzyloxy)carbonyl]amino}-5-hydroxy-5-(2-pyridinyl)pentanoate (22). To *N*-oxide **21** (95 mg, 0.27 mmol) in CH_2Cl_2 (2.5 mL) at rt under nitrogen was added trifluoroacetic anhydride (695 mg, 3.32 mmol) over 5 min. The solution was stirred overnight at rt and then concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (0.7 mL) and saponified with aq. Na_2CO_3 (2 M, 2 mL) for 3 h. The organic layer was separated and the aqueous layer washed with CH_2Cl_2 (10 mL) and the combined organic layers were dried, filtered and concentrated in vacuo to give the crude product which was purified by column chromatography eluting with EtOAc to give the title compound **22** (59 mg, 62%, approx. 1:1 mixture of diastereomers) as a colourless oil, R_f 0.25 (EtOAc); IR (film) 3333, 3033, 2953, 2864, 1746, 1731, 1716, 1595, 1538, 1455, 1436, 1215 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.60–2.14 (4H, m), 3.70 (3H, s), [†]3.72 (3H, s), 3.90–4.32 (1H, m), 4.33–4.50 (1H, m), 4.71–4.83 (1H, m), 5.00–5.17 (2H, m), 5.53 (1H, d, *J*=8.0 Hz), 5.64 (1H, d, J=8.0 Hz), 7.15–7.28 (2H, m), 7.29–7.40 (5H, m), 7.66 (1H, td, *J*=8.0, 2.0 Hz), 8.51 (1H, d, *J*=4.5 Hz); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 28.4, 33.9, 52.3, 53.5, 53.8, 66.9, 71.5, 71.9, 120.2, 122.4, 128.0, 128.1, 128.4, 136.2, 136.9, 148.0, 148.1, 156.0, 161.2, 172.8; CIMS *m/z* 359 (MH^+, 15), 91 (100); HRCIMS Found: MH^+ 359.1607. $C_{19}H_{22}N_2O_5$ requires MH, 359.1607.

4.2.13. (2*S*)-2-{[(Benzyloxy)carbonyl]amino}-5-oxo-5-(2-pyridinyl)pentanoic acid (23). (i) Manganese dioxide (activated, 66 mg, 0.75 mmol) was added in 2 portions to a stirred solution of alcohol **22** (47 mg, 0.13 mmol) over 20 min at rt under nitrogen. The reaction mixture was stirred overnight, then filtered through Celite and concentrated in vacuo. The crude product was purified by column chromatography eluting with light petroleum–EtOAc (1:2) to afford a colourless solid (33 mg, 71%).

(ii) LiOH (0.5 M in H_2O, 80 μmol, 0.16 mL) was added to a stirred solution of the product (28 mg, 79 μmol) from step (i) in THF (0.4 mL) at 0°C and warmed to rt. The mixture was stirred for 30 min and then aqueous sodium dihydrogenorthophosphate (1 M, 0.5 mL) was added and the mixture extracted with EtOAc (3×5 mL). The organic layer was dried, filtered and concentrated in vacuo to give the crude product which was purified by column chromatography eluting with EtOAc to afford **23** (22 mg, 82%) as a colourless oil, R_f 0.14 (EtOH–EtOAc, 1:9); $[\alpha]_D$=−5.1 (*c* 0.9, $CHCl_3$); IR (film) 3422, 2944, 1731, 1699, 1682, 1538, 1404, 1345, 1216 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 2.18–2.43 (2H, m), 3.22–3.51 (2H, m), 4.50–4.63 (1H, m), 5.07 (2H, s), 5.95 (1H, d, *J*=8.0 Hz), 7.20–7.41 (5H, m), 7.46–7.51 (1H, m), 7.83 (1H, t, *J*=7.5 Hz), 8.02 (1H, d, *J*=7.5 Hz), 8.67 (1H, d, *J*=4.0 Hz), 11.0 (1H, br s); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 26.4, 33.9, 53.4, 67.1, 122.5, 127.7, 128.2, 128.5, 128.6, 136.3, 137.8, 148.7, 152.5, 156.3, 174.9, 200.0; CIMS *m/z* 343 (MH^+, 15), 325 (100); HRCIMS Found: MH^+ 343.1304. $C_{18}H_{18}N_2O_5$ requires MH, 343.1294.

4.2.14. (2*S*)-5-(2-Pyridinyl)-2-pyrrolidinecarboxylic acid (24). Carbamate **23** (15 mg, 44 μmol) in EtOH (1 mL) was exposed to an atmosphere of hydrogen gas (introduced by balloon after evacuation of a nitrogen atmosphere) in the presence of Pd–C (10%, 2 mg) at rt overnight. The reaction mixture was filtered through Celite and concentrated in vacuo to give the title compound **24** (8 mg, 95%, ca. 1:1 mixture of diastereomers) as a white solid, mp 170–172°C; IR (film) 3484, 2971, 2926, 2858, 1716, 1699, 1455 cm^{-1}; ^1H NMR (500 MHz, D_2O) δ 1.85–2.05 (4H, m), 3.90–3.98 (1H, m), 5.04–5.11 (1H, m), 7.79–7.89 (2H, m), 8.38–8.46 (1H, m), 8.51–8.58 (1H, m); ^{13}C NMR (125 MHz, D_2O) δ 25.7, 31.8, [†]31.9, 52.6, 52.7, 68.6, 124.5, 126.1, 140.5, 147.2, 156.9, 171.9; CIMS *m/z* 193 (MH^+, 100), 106 (34); HRCIMS Found: MH^+ 193.0978. $C_{10}H_{12}N_2O_2$ requires MH, 193.0977.

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