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Synthesis of β^2-homophenylalanine derivatives by Negishi cross-coupling reactions

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Abstract

Three approaches to the synthesis of β^2-homophenylalanine derivatives using Negishi cross-coupling reaction are reported. In the first two approaches, two protected α-iodomethyl-β-amino esters are each converted into the corresponding organozinc iodides, which then undergo Pd-catalysed cross-coupling with aromatic halides to give β^2-homophenylalanine derivatives, and the X-ray crystal structure of one product is reported. Alternatively, Negishi cross-coupling of the zinc reagent derived from *N*-benzyl 3-iodomethyl azetidin-2-one and aryl halides gave 3-benzylazetidin-2-ones, masked β^2-homophenylalanine derivatives. The X-ray crystal structure of 1-benzyl-3-[(*p*-toluenesulfonyloxy)-methyl]-azetidin-2-one confirms the structural assignment.

1. Introduction

The synthesis of amino acids continues to receive much interest due to their presence in compounds of biological importance. β-Amino acids are less abundant in nature than α-amino acids, although they are an important class of compound present in various natural products.[1–4] Peptides containing β-amino acid residues form stable secondary structures and are more resistant to enzymatic metabolism than their α-amino acid counterparts.[2,3,5–9] In addition, β-amino acids display interesting pharmacological properties and are useful synthetic precursors to β-lactams.[1,10] β-Amino acids can be grouped according to the position of the side-chain, as summarised by Seebach as β^2-, β^3- and $\beta^{2,3}$-amino acid[2,3] (Fig. 1).

Synthetic methods for the preparation of β-amino acids have been comprehensively reviewed.[2–4,11–14] While the synthesis of β^3-amino acids by homologation of α-amino acids is well established, there is no simple equivalent process for the conversion of α-amino acids into β^2-amino acids, and routes to β^2-amino acids are in general less well-developed than those to β^3-amino acids. Previously, in the context of the synthesis of β^3-amino acids, we reported that alkyl iodides obtained from a selectively reduced L-aspartic acid derivative underwent Pd-catalysed cross-coupling with aryl iodides and acid chlorides to give β^3-substituted amino acid derivatives.[15,16] We now wish to report the application of organozinc chemistry[17] to the synthesis of racemic β^2-substituted amino acid derivatives.

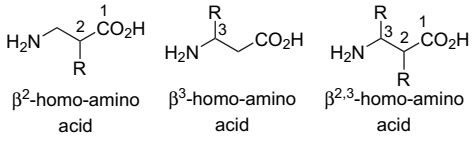

Figure 1. β-Homo-amino acids.

2. Results and discussion

We considered that the required β^2-substituted amino acid framework **1** could be prepared by the conjugate addition of a protected amine **2** to readily available methyl

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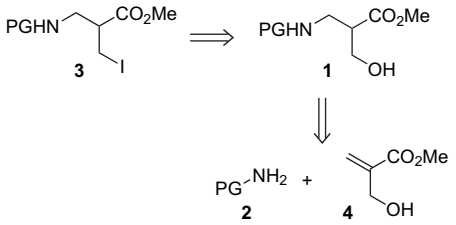
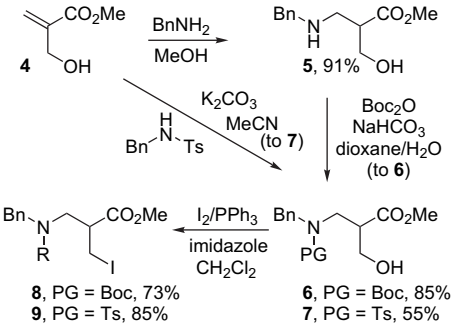
(2-hydroxymethyl)propenoate **4** (Scheme 1). Conversion of the hydroxymethyl group into the corresponding alkyl iodide derivative **3** would afford the precursor for the Negishi cross-coupling reaction.



Scheme 1. Strategy for β^2-substituted amino acid synthesis.

Methyl (2-hydroxymethyl)propenoate **4** was synthesised from trimethyl phosphonoacetate and formaldehyde, following the procedure for the synthesis of the analogous ethyl ester.[18] Conjugate addition of benzylamine to **4** in methanol gave the corresponding amino alcohol **5** in good yield (Scheme 2).[19,20] Selective protection of the secondary amine was performed using Boc_2O in basic aqueous solution to afford the protected amino alcohol **6** in 85% isolated yield. As an alternative, conjugate addition of tosyl-protected benzylamine to ester **4** gave the protected amino alcohol **7** directly (55%). Treatment of each of the amino alcohols **6** and **7** with iodine, PPh_3 and imidazole[21] gave the corresponding alkyl iodides **8** and **9** in good yields after purification by column chromatography (Scheme 2).



Scheme 2. Synthesis of β^2-iodomethyl amino acid derivatives **8** and **9**.

The alkyl iodides **8** and **9** were each converted into the corresponding organozinc iodides using zinc activated with catalytic I_2 in DMF.[22] Palladium-catalysed cross-coupling of each of the zinc reagents with aromatic halides using $Pd_2(dba)_3$/P(*o*-tol)$_3$, gave β^2-homophenylalanine derivatives in moderate to good yields over two steps from the starting alkyl iodides (Scheme 3, Table 1).

Scheme 3. Synthesis of β^2-homophenylalanine derivatives.

Table 1
Synthesis of β^2-homophenylalanine derivatives **10** and **11**

Ar	X	Product	Yield (%)	Product	Yield[a] (%)
Ph	I	**10a**	72	**11a**	75 (78)[b]
Ph	Br	**10a**	62	**11a**	76
4-MeO–C_6H_4	I	**10b**	77	**11b**	89
4-O_2N–C_6H_4	I	**10c**	24 (45)[c]	**11c**	60
3-O_2N–C_6H_4	I	**10d**	20 (43)[c]	**11d**	54
4-HO–C_6H_4	I	**10e**	40	**11e**	62
3-HO–C_6H_4	I	**10f**	50	**11f**	62

[a] Refers to products obtained after column chromatography.
[b] Undistilled DMF used directly.
[c] Excess zinc removed before cross-coupling, see Section 4.1.3.

Superior yields were obtained in the Negishi cross-coupling reaction of the zinc reagent derived from sulfonyl-protected nitrogen series **9** compared to the corresponding Boc-protected amino acid derivatives **8** (Table 1). Protonation of the organozinc iodide is a competing reaction pathway and results in the formation of protected β^2-homoalanine, which was isolated in instances of low yields.

Cross-coupling of the zinc reagent derived from the tosyl-derivative **9** with both PhI and PhBr to give **11a** was equally effective (Table 1), whereas the reaction of the zinc reagent derived from the Boc-derivative **8** was somewhat less efficient with PhBr than with PhI. This is reminiscent of the behaviour of relatively unreactive α-amino acid-derived organozinc reagents, which react with aryl bromides in lower yield than they do with the corresponding aryl iodides.[23]

The crystal structure of the coupled product **11a** was obtained (Fig. 2), which showed that one *ortho*-proton of the newly introduced phenyl group is located directly above the aromatic ring of the *N*-benzyl substituent. This conformational effect also appears to persist to some extent in solution, as evidenced by the chemical shift of the same *ortho*-protons in each of the coupled products **11a–f**. Although the bulk sample of adduct **11a** was racemic, the crystal was homochiral indicating that the compound crystallised as a conglomerate.

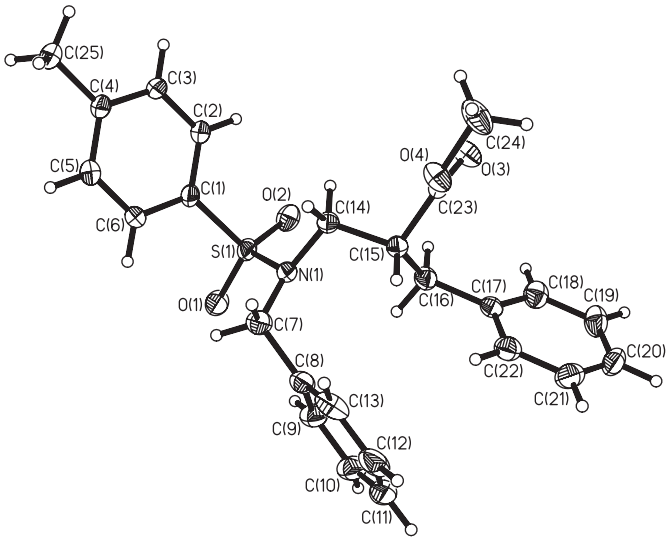
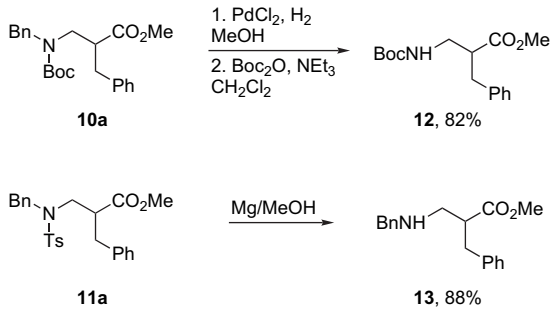


Figure 2. Coupled Product **11a**, showing the proton at C(22).

The poor yields of the nitrophenyl derivatives **10c** and **10d**, obtained by reaction of zinc reagent derived from the alkyl iodide **8**, are due to competing reduction of the NO_2 group of the product by excess zinc used in the reaction. Removal of the excess zinc prior to the Negishi coupling reaction gave significantly improved yields.

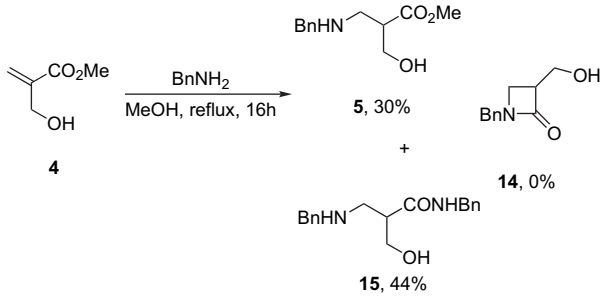
Previous studies had shown that unprotected phenols can be tolerated in the Negishi reaction,[24] and this proved to the case here also. Better yields were obtained in the cross-coupling of the zinc reagent derived from the sulfonyl-protected iodide **9** with both 3- and 4-iodophenol compared with the Boc-analogue **8**, which once more testifies to the greater reactivity of the zinc reagent derived from the sulfonyl-protected iodide **9**. Since the reaction tolerates the presence of an unprotected phenol, we also investigated the effect of residual water in the solvent. DMF used in these coupling reactions was normally distilled from CaH_2 and stored over 4 Å molecular sieves. However, when the reaction was conducted using DMF as supplied, the product was obtained in 78% isolated yield. This preliminary result demonstrates that DMF may not need to be rigorously dried prior to use in the cross-coupling reaction.

Removal of the benzyl group from adduct **10a** was performed using $PdCl_2$ under an atmosphere of H_2, following a procedure previously reported for a similarly protected amine.[25] In the event, partial removal of the Boc-protecting group also occurred, possibly due to in situ generation of HCl. This observation demonstrates the potential for removal of both nitrogen protecting groups in one synthetic step. However, for ease of isolation and purification the crude reaction mixture was treated with Boc_2O to give the Boc-protected β^2-homophenylalanine derivative **12** (82%). Although use of the sulfonamide group gave good yields of highly crystalline products in the Negishi cross-coupling reaction, cleavage of the sulfonyl protecting group can require harsh reaction conditions that may result in decomposition. Pleasingly, however, treatment of adduct **11a** with Mg/MeOH, previously used for the deprotection of sulfonyl aziridines[26] and applied to piperidines,[27] cleaved the sulfonamide group to give the protected β^2-homophenylalanine derivative **13** (88%) (Scheme 4).



Scheme 4. Deprotection of coupled products.

An alternative protecting group strategy was also investigated, in which the β^2-amino acid derivative was masked as a β-lactam derivative. This approach offered the potential benefit of simplicity. The synthesis of the required hydroxymethyl β-lactam precursor **14** by heating a solution of benzylamine (4 equiv) and ethyl (2-hydroxymethyl)propenoate (1 equiv) in dry methanol had been reported.[19,20] Unfortunately, in our hands, use of the same reaction conditions with the methyl ester **4**, did not give any of the desired β-lactam **14**, but instead a mixture of product **5** already isolated, together with the 2:1 adduct **15**. The structure of this latter compound was unambiguously determined by X-ray crystallography (Scheme 5, Fig. 3).



Scheme 5. Attempted direct formation of β-lactam **14**.

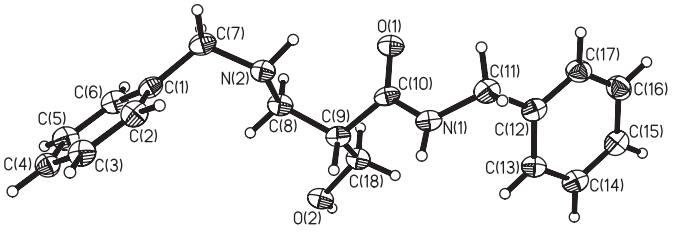


Figure 3. Product **15** arising from 1,2- and 1,4- addition of benzylamine to **4**.

Using a procedure previously reported for the cyclisation of a very similar substrate,[28] treatment of the amino alcohol **5** with ^{t}BuMgCl in THF gave the β-lactam **14** (67%). The physical and spectroscopic data for the β-lactam **14** differed from that previously reported,[20] notably in the IR stretching frequency of the carbonyl group (we observed 1729 cm^{-1}, compared with the reported value of 1710 cm^{-1})[20] and in the physical state of the compound. The identity of our material was confirmed by conversion into the crystalline tosylate **16** whose structure was determined by X-ray crystallography (Fig. 4). The iodo β-lactam **17** was obtained either by treatment of the hydroxymethyl β-lactam **14** with iodine and PPh_3 (76%), or by treatment of the tosylate **16** with NaI (89%) (Scheme 6).

Conversion of the iodo β-lactam **17** into the corresponding zinc reagent proceeded smoothly, and subsequent Pd(0)-catalysed cross-coupling with aromatic halides gave the expected 3-benzylazetidin-3-ones **18a–f** (Scheme 7, Table 2). 3-Methyl azetidin-2-one, resulting from protonation of the organozinc iodide intermediate, was also recovered from these reactions.

Although Negishi reactions of organozinc reagents derived from azetidines have been reported,[29] the results reported herein appear to be the first examples of an organozinc halide derived from a β-lactam undergoing a Negishi reaction.

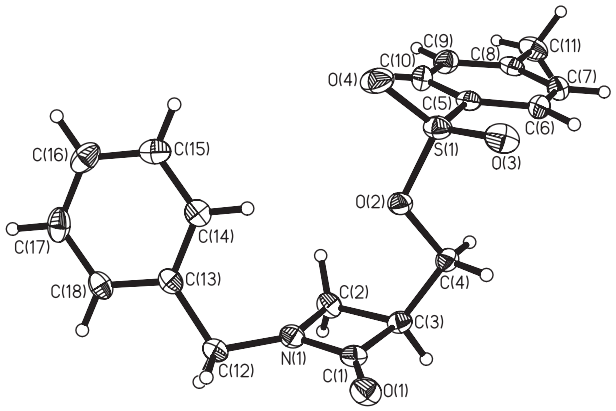
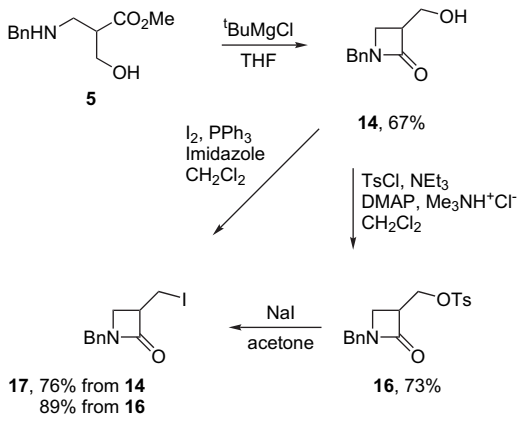
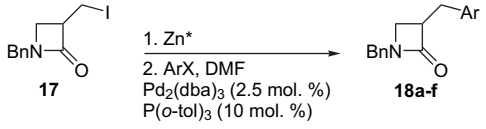


Figure 4. β-Lactam **16**.



Scheme 6. Synthesis of the iodo β-lactam **17**.



Scheme 7. Synthesis of 3-benzylazetidin-2-ones.

Table 2
Synthesis of 3-benzylazetidin-2-ones **18**

Entry	Ar	X	Product	Yield[a] (%)
1	Ph	I	**18a**	72
2	Ph	Br	**18a**	68
3	4-MeO–C_6H_4	I	**18b**	65
4	4-O_2N–C_6H_4	I	**18c**	44
5	3-O_2N–C_6H_4	I	**18d**	47
6	4-HO–C_6H_4	I	**18e**	56
7	3-HO–C_6H_4	I	**18f**	52

[a] Refers to products obtained after column chromatography.

3. Conclusions

In this paper, we have shown that racemic β^2-substituted amino acid derivatives **10**, **11** and **18** can be prepared from a readily available β-amino ester precursor, making use of the Negishi cross-coupling with aromatic halides, including unprotected iodophenols.

4. Experimental

4.1. General experimental

All reagents used were purchased from commercial sources and used without further purification. All moisture/air sensitive reactions were conducted under a positive pressure of nitrogen in flame dried or oven dried glassware. Water is demineralised water and all solvents used were HPLC grade or distilled. Petroleum ether refers to the fraction which boils in the range 40–60 °C. Dry DMF was distilled from calcium hydride and stored over 4 Å molecular sieves.

Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker DRX-500 NMR spectrometer at room temperature or at the stated temperature. Chemical shifts were measured relative to residual solvent and are expressed in parts per million (δ). Coupling constants (J) are given in hertz and the measured values are rounded to the nearest 0.1 Hz and are not rationalised. High-resolution mass spectra were recorded using a MicroMass LCT operating in electrospray (ES) mode or Kratos MS 25 or MS 80 for electro impact (EI). Chemical analyses were performed using a Perkin Elmer 2400 CHN elemental analyser. Infra-red spectra were recorded on a Perkin Elmer Paragon 100 FTIR spectrophotometer (ν_{max} in cm^{-1}) as thin films using NaCl plates. Melting points were determined using a Linkam HFS91 heating stage, used in conjunction with a TC92 controller and are uncorrected.

Thin layer chromatography (TLC) was performed on precoated plates (0.2 mm, Merck DC-alufolien Kieselgel 60 F_{254}) and compounds were visualised by UV light (254 nm), ninhydrin solution (5% in MeOH) or $KMnO_4$. Column chromatography was performed using silica gel 60 from BDH Lab or Davisil Fluorochem.

4.1.1. Iodination procedure

A solution of the alcohol (10.5 mmol) in dry CH_2Cl_2 (20 mL) was added dropwise by syringe over 5 min to a stirred solution of triphenylphosphine (2.90 g, 11.07 mmol), imidazole (0.75 g, 11.07 mmol) and iodine (2.81 g, 11.07 mmol) in dry CH_2Cl_2 (30 mL) under nitrogen at room temperature. The reaction continued until TLC analysis indicated complete consumption of starting material. The precipitate was removed by filtration and the filtrate was washed with aqueous sodium thiosulfate solution (2×30 mL, 1 M) and brine, dried ($MgSO_4$) and evaporated under reduced pressure to afford the crude product, which was purified by silica gel column chromatography.

4.1.2. Cross-coupling reaction: procedure A (one-pot)

Zinc dust (195 mg, 3.0 mmol, 6.0 equiv) was placed in a dry 25 mL round bottom flask, with sidearm, containing a rugby ball shaped magnetic stirrer. The flask was flushed with nitrogen and dry DMF (0.2 mL) added under nitrogen via syringe followed by catalytic iodine (40 mg, 0.15 mmol, 0.3 equiv). Effervescence was observed and the DMF changed from colourless to yellow and back again. A solution of the appropriate alkyl iodide (0.5 mmol) was dissolved in DMF

(0.3 mL) under nitrogen and transferred to the activated zinc suspension via syringe. The solution was stirred at room temperature and the insertion proceeded with a noticeable exotherm. When the solution had cooled $Pd_2(dba)_3$ (11.0 mg, 0.0125 mmol, 2.5 mol %), P(*o*-tol)$_3$ (15 mg, 0.05 mmol, 10 mol %) and the aryl iodide (1.3 equiv relative to the alkyl iodide) were added to the flask and the reaction mixture was left at room temperature overnight. The crude reaction mixture was applied directly to a silica gel chromatography column to afford the purified cross-coupled product.

4.1.3. Cross-coupling reaction: procedure B (two-pot)

As *procedure A* except once the reaction had cooled after zinc insertion, the solution was removed via syringe to a separate flask to which were added $Pd_2(dba)_3$ (11.0 mg, 0.0125 mmol, 2.5 mol %), P(*o*-tol)$_3$ (15 mg, 0.05 mmol, 10 mol %) and the aryl iodide (1.3 equiv relative to the alkyl iodide). The reaction mixture was left at room temperature overnight and the crude reaction mixture was applied directly to a silica gel chromatography column to afford the purified cross-coupled product.

4.1.3.1. Methyl 2-(hydroxymethyl)propenoate ***4***. Following a previously reported procedure for the ethyl ester,[18] a saturated aqueous solution of K_2CO_3 (6.63 g, 48 mmol) was slowly added (30 min) to a rapidly stirred solution of trimethyl phosphonoacetate (5.46 g, 30 mmol) and formaldehyde (37% w/w solution, 10 mL, 117 mmol) at room temperature, which produced an exotherm. After the addition the reaction mixture was stirred at room temperature for a further 1 h before being quenched with H_2O (30 mL). The aqueous phase was extracted with CH_2Cl_2 (3×30 mL) and the organic fractions combined, washed with brine (2×30 mL), dried ($MgSO_4$) and evaporated under reduced pressure. Purification by silica gel column chromatography (petrol/EtOAc, gradient from 20–100% EtOAc) gave the ester **4** (1.9 g, 55%) as a colourless oil. R_f 0.6 (EtOAc); (Found: C, 51.6; H, 7.3. $C_5H_8O_3$ requires C, 51.7; H, 6.9); ν_{max} (film)/cm^{-1} 3410 br, 1715 and 1636; δ_H (500 MHz, $CDCl_3$) 2.99 (1H, t, *J* 6.3, CH_2OH), 3.73 (3H, s, CO_2CH_3), 4.27 (2H, d, *J* 6.2, CH_2OH), 5.81 (1H, d, *J* 2.4, H_AH_B=C) and 6.21 (1H, d, *J* 2.4, H_AH_B=C); δ_C (126 MHz, $CDCl_3$) 52.2, 62.4, 126.0, 139.7, 167.1; *m/z* (EI) found: M$^+$, 116.0474. $C_5H_8O_3$ requires M$^+$ 116.0473, 117 (16%, MH$^+$), 116 (50, M$^+$), 99 (100, M$^+$–OH). Spectroscopic data consistent with that previously reported.[30]

4.1.3.2. Methyl 2-[(N-benzyl-amino)-methyl]-3-hydroxy-propanoate ***5***. By minor modification of the literature procedure,[18] benzylamine (1.1 mL, 10 mmol) was added to a solution of the ester **4** (1.0 g, 8.6 mmol) in MeOH (HPLC grade, but not dried, 20 mL). The reaction mixture was stirred at room temperature for 16 h before being concentrated under reduced pressure to give, without the need for purification, the amino alcohol product **5** (1.75 g, 91% yield) as a colourless oil. R_f 0.1 (EtOAc); ν_{max} (film)/cm^{-1} 3324 br, 2952 and 1732; δ_H (500 MHz, $CDCl_3$) 2.68–2.73 (1H, m, CH), 2.91 (1H, dd, *J* 12.1 and 4.4, CHCH_AH$_B$N), 3.16 (1H, dd, *J* 12.1 and 5.7, CHCH$_A$$H_B$N), 3.71 (3H, s, CO_2CH_3), 3.78–3.79 (2H, m, NHCH_2Ph), 3.96 (1H, dd, *J* 10.9 and 3.8, CH_AH$_B$OH), 4.02 (1H, dd, *J* 10.9 and 5.3, CH$_A$$H_B$OH) and 7.22–7.33 (5H, m, Ar); δ_C (126 MHz, $CDCl_3$) 45.8, 49.7, 51.9, 53.9, 64.7, 127.3, 127.6, 128.2, 128.4, 128.5, 138.9 and 173.5; *m/z* (EI) 223 (M$^+$, 2%) and 91 ($C_6H_7^+$, 100). Found M$^+$ 223.1208. $C_{12}H_{17}NO_3$ requires 223.1208.

4.1.3.3. Methyl 2-{[N-benzyl-(tert-butoxycarbonyl)-amino]-methyl}-3-hydroxy-propanoate ***6***. Using conditions originally reported for a vicinal amino alcohol,[31] a solution of $NaHCO_3$ (1.13 g, 13.4 mmol) in H_2O (20 mL) was added to a stirred solution of amino alcohol **5** (2.99 g, 13.4 mmol) in dioxane (40 mL) at room temperature. After 10 min Boc_2O (2.95 g, 13.4 mmol) was added and the pH monitored and adjusted to pH 10 as necessary with the addition of $NaHCO_3$. After 18 h the reaction mixture was concentrated under reduced pressure and EtOAc and H_2O were added. The organic layer was separated, washed with brine (30 mL), dried (Na_2SO_4) and the solvent removed under reduced pressure to give, without the need for further purification, the Boc-benzyl protected amino alcohol **6** (3.64 g, 85%) as a colourless oil. R_f 0.35 (petrol/EtOAc, 1:1); ν_{max} (film)/cm^{-1} 3445 br, 2976, 1732 and 1694. At 22 °C the ^{1}H NMR of this compound showed significant rotameric behaviour. Upon heating to 61 °C most peaks sharpened, but the signals for CH and CHCH$_A$$H_B$N remained hidden due to broadening. Their presence was noted by the baseline integrals (1H between 2.5–3.5 and 1H between 3.4–4.0); δ_H (500 MHz, $CDCl_3$, 61 °C) 1.48 (9H, s, C(CH$_3$)$_3$), 2.77 (1H, br s, OH), 3.51 (1H, dd, *J* 14.6 and 5.9, CHCH_AH$_B$N), 3.70 (3H, s, CO_2CH_3), 3.74 (1H, dd, *J* 11.7 and 4.9, CH_AH$_B$OH), 3.85 (1H, dd, *J* 11.7 and 4.9, CH$_A$$H_B$OH), 4.45 (2H, s, NC$H_2$Ph) and 7.22–7.35 (5H, m, Ar); δ_C (126 MHz, $CDCl_3$, 22 °C) 28.3, 44.2, 44.8, 45.9, 46.6, 50.4, 51.4, 51.9, 59.8, 81.0, 127.2, 127.4, 127.7, 128.0, 128.6, 137.9, 157.0 and 173.2. Upon heating rotameric peaks coalesced to give the expected number of signals; δ_C (126 MHz, $CDCl_3$, 61 °C) 28.2, 44.7, 46.5, 51.3, 51.6, 60.2, 80.6, 127.2, 128.0, 128.5, 137.9, 156.5 and 173.2; *m/z* (ES) 346 (MNa$^+$, 98%) and 323 (M$^+$, 100). Found MNa$^+$ 346.1646. $C_{17}H_{25}NO_5Na$ requires 346.1630.

4.1.3.4. Methyl 2-{[N-benzyl-(tert-butoxycarbonyl)-amino]-methyl}-3-iodo-propanoate ***8***. Following the *iodination procedure*, alcohol **6** (3.39 g, 10.5 mmol) gave, after purification by silica gel column chromatography (petrol/EtOAc, gradient from petrol to 80% EtOAc), the alkyl iodide **8** (3.30 g, 73%) as a colourless oil. R_f 0.75 (petrol/EtOAc, 1:1); ν_{max} (film)/cm^{-1} 2977, 1740 and 1698; δ_H (500 MHz, $CDCl_3$, 61 °C) 1.49 (9H, s, C(CH$_3$)$_3$), 3.13–3.20 (1H, m, CHCH$_2$I), 3.25–3.37 (2H, m, CHCH_2I), 3.40–3.52 (2H, m, CHCH_2N), 3.74 (3H, s, CO_2CH_3), 4.45 (1H, d, *J* 15.6, NCH_AH$_B$Ph), 4.53 (1H, d, *J* 15.6, NCH$_A$$H_B$Ph) and 7.23–7.36 (5H, m, Ar); δ_C (126 MHz, $CDCl_3$, 22 °C) 0.0, 0.79, 25.9, 26.6, 26.7, 42.9, 45.2, 45.6, 46.9, 47.6, 48.9, 49.8, 50.1, 50.3, 50.5, 78.7, 125.4, 125.5, 125.6, 125.7, 126.0, 126.7, 126.8, 127.4, 136.2, 153.9, 154.1 and 170.5. More signals than expected in ^{13}C NMR due

to presence of rotamers; *m/z* (ES) 456 (MNa^+, 55%), 334 ($MH^+-CO_2(CH_3)_3$, 97) and 268 (100). Found MNa^+ 456.0656. $C_{17}H_{24}INO_4Na$ requires 456.0648.

*4.1.3.5. Methyl 2-{[N-benzyl-(tert-butoxycarbonyl)-amino]-methyl}-3-phenylpropanoate **10a**.* Following *procedure A*, alkyl iodide **8** (217 mg, 0.5 mmol) and iodobenzene (0.86 μL, 0.65 mmol) gave, after purification by silica gel column chromatography (petrol/EtOAc, gradient from petrol to 50% EtOAc), the β^2-amino acid derivative **10a** (138 mg, 72%) as a pale orange oil. R_f 0.7 (petrol/EtOAc, 1:1); ν_{max} (film)/cm^{-1} 2977, 1738 and 1697; δ_H (500 MHz, $CDCl_3$, 61 °C) 1.48 (9H, s, $C(CH_3)_3$), 2.63–2.84 (1H, m, $CHCH_AH_BPh$), 2.91 (1H, dd, *J* 13.8 and 8.8, $CHCH_AH_BPh$), 3.07–3.18 (1H, m, CH), 3.41–3.52 (2H, m, $CHCH_2N$), 3.60 (3H, s, CO_2CH_3), 4.35 (1H, d, *J* 15.5, NCH_AH_BPh), 4.46–4.60 (1H, m, NCH_AH_BPh) and 7.11–7.35 (10H, m, Ar); δ_C (126 MHz, $CDCl_3$, 22 °C) 27.7, 28.0, 28.4, 36.2, 36.5, 46.4, 47.0, 48.3, 49.1, 50.5, 51.5, 51.8, 80.2, 126.5, 127.2, 127.5, 127.9, 128.1, 128.5, 128.7, 129.1, 138.0, 138.5, 138.7, 155.8 and 174.8. More signals than expected in ^{13}C NMR due to presence of rotamers; *m/z* (ES) 384 (MH^+, 77%) and 328 ($MH^+-C_4H_9$, 100). Found MH^+ 384.2170. $C_{23}H_{30}NO_4$ requires 384.2175.

In addition, following *procedure A*, alkyl iodide **8** (217 mg, 0.5 mmol) and bromobenzene (68.5 μg, 0.65 mmol) gave, after purification as previously described, the β^2-amino acid derivative **10a** (119 mg, 62%) as a pale orange oil, spectroscopically consistent with that previously reported herein.

*4.1.3.6. Methyl 2-{[N-benzyl-(tert-butoxycarbonyl)-amino]-methyl}-3-(p-methoxyphenyl)-propanoate **10b**.* Following *procedure A*, alkyl iodide **8** (217 mg, 0.5 mmol) and 4-iodoanisole (152 mg, 0.65 mmol) gave, after purification by silica gel column chromatography (petrol/EtOAc, gradient from petrol to 80% EtOAc), the β^2-amino acid derivative **10b** (158 mg, 77% yield) as a pale orange oil. R_f 0.5 (petrol/EtOAc, 1:1); ν_{max} (film)/cm^{-1} 2976, 1737 and 1695; δ_H (500 MHz, $CDCl_3$, 61 °C) 1.48 (9H, s, $C(CH_3)_3$), 2.63–2.74 (1H, m, $CHCH_AH_BAr$), 2.85 (1H, dd, *J* 13.9 and 8.8, $CHCH_AH_BAr$), 3.01–3.17 (1H, m, CH), 3.41–3.44 (2H, m, $CHCH_2N$), 3.61 (3H, s, CO_2CH_3), 3.80 (3H, s, $ArCH_3$), 4.34 (1H, d, *J* 15.5, NCH_AH_BPh), 4.45–4.60 (1H, m, NCH_AH_BPh), 7.78–7.87 (2H, m, Ar), 7.00–7.09 (2H, m, Ar) and 7.18–7.35 (5H, m, Ar); δ_C (126 MHz, $CDCl_3$, 22 °C) 28.4, 35.4, 46.7, 47.3, 48.4, 49.0, 50.5, 51.7, 55.2, 80.1, 113.9, 127.2, 127.8, 128.5, 129.7, 130.6 and 174.9. More signals than expected in ^{13}C NMR due to presence of rotamers; *m/z* (ES) 414 (MH^+, 7%), 413 (M^+, 23) and 120 (100); *m/z* (EI) found M^+ 413.2186. $C_{24}H_{31}NO_5$ requires 413.2202.

*4.1.3.7. Methyl 2-{[N-benzyl-(tert-butoxycarbonyl)-amino]-methyl}-3-(p-nitrophenyl)-propanoate **10c**.* Following *procedure A*, alkyl iodide **8** (217 mg, 0.5 mmol) and 1-iodo-4-nitro benzene (162 mg, 0.65 mmol) gave, after purification by silica gel column chromatography (petrol/EtOAc, gradient from petrol to 100% EtOAc), the β^2-amino acid derivative **10c** (52 mg, 24%) as a pale orange oil; R_f 0.30 (petrol/EtOAc, 3:2); ν_{max} (film)/cm^{-1} 2977, 1738 (C=O), 1694, 1521 and 1347 s; δ_H (500 MHz, $CDCl_3$, 61 °C) 1.50 (9H, s, $C(CH_3)_3$), 2.78–2.90 (1H, m, $CHCH_AH_BAr$), 2.99 (1H, dd, *J* 13.8 and 9.4, $CHCH_AH_BAr$), 3.07–3.19 (1H, m, CH), 3.42–3.52 (2H, m, $CHCH_2N$), 3.60 (3H, s, CO_2CH_3), 4.38 (1H, d, *J* 15.6, NCH_AH_BPh), 4.51 (1H, d, *J* 15.5, NCH_AH_BPh), 6.99–7.62 (7H, m, Ar) and 8.11–8.14 (2H, m, Ar); δ_C (126 MHz, $CDCl_3$, 22 °C) 28.4, 35.9, 46.0, 46.6, 48.7, 49.3, 50.8, 51.8, 51.9, 80.5, 123.7, 127.2, 127.4, 127.8, 128.0, 128.6, 129.6, 138.1, 146.5, 146.7, 155.7 and 173.9. More signals than expected in ^{13}C NMR due to presence of rotamers; *m/z* (ES) 451 (MNa^+, 5%), 329 ($MH^+-C_5H_8O_2$, 100). Found MNa^+ 451.1850. $C_{23}H_{28}N_2O_6Na$ requires 451.1845.

Following *procedure B*, alkyl iodide **8** (217 mg, 0.5 mmol) and 1-iodo-4-nitro benzene (162 mg, 0.65 mmol) gave, after purification as previously described, the β^2-amino acid derivative **10c** (96 mg, 45% yield) as a pale orange oil, spectroscopically consistent with that previously reported herein.

*4.1.3.8. Methyl 2-{[N-benzyl-(tert-butoxycarbonyl)-amino]-methyl}-3-(m-nitrophenyl)-propanoate **10d**.* Following *procedure A*, alkyl iodide **8** (217 mg, 0.5 mmol) and 1-iodo-3-nitro benzene (162 mg, 0.65 mmol) gave, after purification by silica gel column chromatography (petrol/EtOAc, gradient from petrol to 100% EtOAc), the β^2-amino acid derivative **10d** (42 mg, 20%) as a pale orange oil. R_f 0.30 (petrol/EtOAc, 3:2); ν_{max} (film)/cm^{-1} 3931, 1737, 1695, 1531 and 1352 s; δ_H (500 MHz, $CDCl_3$, 61 °C) 1.50 (9H, s, $C(CH_3)_3$), 2.80–2.92 (1H, m, $CHCH_AH_BAr$), 3.00 (1H, dd, *J* 13.8 and 9.5, $CHCH_AH_BAr$), 3.07–3.18 (1H, m, CH), 3.44–3.54 (2H, m, $CHCH_2N$), 3.61 (3H, s, CO_2CH_3), 4.40 (1H, d, *J* 15.5, NCH_AH_BPh), 4.52 (1H, d, *J* 15.4, NCH_AH_BPh), 7.03–7.67 (7H, m, Ar), 7.97–7.99 (1H, m, Ar) and 8.06–8.09 (1H, m, Ar); δ_C (126 MHz, $CDCl_3$, 22 °C) 28.4, 35.7, 46.3, 46.8, 48.6, 49.2, 50.7, 51.7, 51.9, 80.5, 121.7, 123.6, 127.2, 127.4, 127.8, 128.6, 129.4, 135.1, 138.1, 140.8, 148.3, 155.7 and 173.9. More signals than expected in ^{13}C NMR due to presence of rotamers; *m/z* (ES) 451 (MNa^+, 13%), 429 (MH^+, 2) and 329 ($MH^+-C_5H_8O_2$, 100). Found MH^+ 429.2044. $C_{23}H_{29}N_2O_6$ requires 429.2026.

Following *procedure B*, alkyl iodide **8** (217 mg, 0.5 mmol) and 1-iodo-3-nitro benzene (162 mg, 0.65 mmol) gave, after purification as previously described, the β^2-amino acid derivative **10d** (92 mg, 43%) as a pale orange oil, spectroscopically consistent with that previously reported herein.

*4.1.3.9. Methyl 2-{[N-benzyl-(tert-butoxycarbonyl)-amino]-methyl}-3-(p-hydroxyphenyl)-propanoate **10e**.* Following *procedure A*, alkyl iodide **8** (217 mg, 0.5 mmol) and 4-iodophenol (143 mg, 0.65 mmol) gave, after purification by silica gel column chromatography (petrol/EtOAc, gradient from petrol to 100% EtOAc), the β^2-amino acid derivative **10e** (80 mg, 40% yield) as a pale orange oil. R_f 0.3 (petrol/EtOAc, 1:1); ν_{max} (film)/cm^{-1} 3362br, 2977, 1735 and 1694; δ_H (500 MHz, $CDCl_3$, 61 °C) 1.48 (9H, s, $C(CH_3)_3$), 2.64–2.72 (1H, m, $CHCH_AH_BAr$), 2.83 (1H, dd, *J* 13.9 and 8.8, $CHCH_AH_BAr$), 3.02–3.10 (1H, m, CH), 3.40–3.45 (2H, m, $CHCH_2N$), 3.60 (3H, s, CO_2CH_3), 4.34 (1H, d, *J* 15.5, NCH_AH_BPh), 4.48–

4.53 (1H, m, NCH_AH_BPh), 4.76 (1H, s, OH), 6.69–6.84 (2H, m, Ar), 6.99 (2H, d, *J* 8.4, Ar) and 7.18–7.34 (5H, m, Ar); δ_C (126 MHz, $CDCl_3$, 22 °C) 28.4, 35.7, 46.7, 47.3, 48.4, 49.1, 50.5, 51.6, 51.8, 80.3, 115.3, 178.2, 127.8, 128.5, 129.9, 130.5, 154.3 and 174.9. More signals than expected in ^{13}C NMR due to presence of rotamers; *m/z* (ES) 422 (MNa^+, 24%), 400 (M^+, 4) and 300 ($MH^+-C_5H_8O_2$, 100). Found MH^+ 400.2113. $C_{23}H_{30}NO_5$ requires 400.2124.

*4.1.3.10. Methyl 2-{[N-benzyl-(tert-butoxycarbonyl)-amino]-methyl}-3-(m-hydroxyphenyl)-propanoate **10f***. Following *procedure A*, alkyl iodide **8** (217 mg, 0.5 mmol) and 3-iodophenol (143 mg, 0.65 mmol) gave, after purification by silica gel column chromatography (petrol/EtOAc, gradient from petrol to 100% EtOAc), the β^2-amino acid derivative **10f** (100 mg, 50% yield) as a pale orange oil. R_f 0.35 (petrol/EtOAc, 1:1); ν_{max} (film)/cm^{-1} 3372 br (OH), 2978, 1738 and 1694; δ_H (500 MHz, $CDCl_3$, 61 °C) 1.48 (9H, s, $C(CH_3)_3$), 2.65–2.71 (1H, m, $CHCH_AH_BAr$), 2.86 (1H, dd, *J* 13.9 and 8.6, $CHCH_AH_BAr$), 3.07–3.15 (1H, m, CH), 3.41–3.49 (2H, m, $CHCH_2N$), 3.61 (3H, s, CO_2CH_3), 4.35 (1H, d, *J* 15.5, NCH_AH_BPh), 4.51 (1H, d, *J* 15.3, NCH_AH_BPh), 5.60 (1H, s, OH), 6.47–6.91 (3H, m, Ar) and 7.10–7.34 (6H, m, Ar); δ_C (126 MHz, $CDCl_3$, 22 °C) 26.6, 27.0, 34.7, 35.0, 44.9, 45.4, 46.9, 47.8, 49.1, 50.2, 50.5, 79.2, 112.3, 114.5, 119.3, 125.9, 126.4, 127.2, 127.3, 128.3, 136.5, 136.7, 138.8, 154.6, 154.9 and 173.7. More signals than expected in ^{13}C NMR due to presence of rotamers; *m/z* (ES) 422 (MNa^+, 3%), 400 (MH^+, 48) and 300 ($MH^+-C_5H_8O_2$, 100). Found MH^+ 400.2104. $C_{23}H_{30}NO_5$ requires 400.2124.

*4.1.3.11. Methyl 2-{[N-(tert-butoxycarbonyl)-amino]-methyl}-3-phenyl-propanoate **12***. Using conditions reported for a similarly Boc-benzyl protected amine,[25] $PdCl_2$ (128 mg, 0.72 mmol) was added to a stirred solution of the Boc-benzyl protected amine **10a** (138 mg, 0.36 mmol) in MeOH (2.1 mL) under a H_2 atmosphere for 4 h. The reaction mixture was filtered through Celite®, washed (3×25 mL MeOH) and concentrated under reduced pressure. Since analysis of the crude ^1H NMR suggested partial removal of the Boc group had occurred, along with debenzylation, the crude product was treated with Boc_2O (88.4 mg, 0.40 mmol, 1.1 equiv) and Et_3N (0.033 mL, 0.40 mmol, 1.1 equiv) in CH_2Cl_2 (10 mL) for 12 h. The reaction mixture was then washed successively with a saturated aqueous solution of $NaHCO_3$ (10 mL) and brine (10 mL), dried ($MgSO_4$) and evaporated under reduced pressure. Purification by silica gel column chromatography (petrol/EtOAc, gradient from petrol to 50% EtOAc), gave the Boc-protected amino ester **12** (87 mg, 82%) as a colourless oil. R_f 0.60 (petrol/EtOAc, 1:1); ν_{max} (film)/cm^{-1} 3375, 2977 and 1715 br; δ_H (500 MHz, $CDCl_3$, 61 °C) 1.46 (9H, s, $C(CH_3)_3$), 2.83 (1H, dd, *J* 12.8 and 6.0, $CHCH_AH_BPh$), 2.90–3.07 (2H, m, $CHCH_AH_BPh$), 3.26–3.35 (1H, m, $CHCH_AH_BN$), 3.35–3.45 (1H, m, $CHCH_AH_BN$), 3.67 (3H, s, CO_2CH_3), 4.79 (1H, s, NH), 7.15–7.25 (3H, m, Ar) and 7.27–7.31 (2H, m, Ar); δ_C (126 MHz, $CDCl_3$, 22 °C) 28.4, 35.9, 41.5, 47.4, 51.8, 79.4, 126.6, 128.5, 128.9, 138.3, 155.8 and 174.7; *m/z* (ES) 316 (MNa^+, 100%) and 194 ($MH^+-CO_2(CH_3)_3$, 78). Found MNa^+ 316.1510. $C_{16}H_{23}NO_4Na$ requires 316.1525.

4.1.3.12. N-Benzyl-4-methylbenzenesulfonamide. Following a procedure previously described for the synthesis of *N*-benzyl-4-bromobenzenesulfonamide,[32] a solution of *p*-toluenesulfonyl chloride (5.7 g, 30 mmol) in CH_2Cl_2 (60 mL) was added to a stirred solution of benzylamine (3.95 mL, 36 mmol) and triethylamine (2.44 mL, 30 mmol) in CH_2Cl_2 (60 mL) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 16 h. The reaction mixture was concentrated under reduced pressure and partitioned between EtOAc and H_2O. The organic extracts were washed successively with HCl (1 N solution, 3×200 mL) and brine (2×150 mL), dried (Na_2SO_4), evaporated under reduced pressure and the crude solid recrystallised from EtOAc/heptane to yield *N*-benzyl-4-methylbenzene-sulfonamide (7.31 g, 91% yield) as white needles. Mp 112.5–113 °C; lit. 111.1 °C[33]; (Found: C, 64.2; H, 5.6; N, 5.2; S, 12.3. $C_{14}H_{15}NO_2S$ requires C, 64.3; H, 5.8; N, 5.4; S, 12.3); *m/z* (EI) 261 (3%, M^+), 106 (100%, M^+-SO_2Ar), 91 (47%, $C_6H_7^+$). Found: M^+, 261.0832. $C_{14}H_{15}NO_2S$ requires M^+ 261.0824. Spectroscopic data consistent with that previously reported.[33,34]

*4.1.3.13. Methyl 2-{[N-benzyl-(p-tolylsulfonyl)-amino]-methyl}-3-hydroxy-propanoate **7***. Using conditions originally reported for the Michael addition of a mono-substituted sulfonamide to an alkyl acrylate,[35,36] K_2CO_3 (0.69 g, 5 mmol) was added to a stirred solution of *N*-benzyl-4-methylbenzenesulfonamide (1.96 g, 7.5 mmol) and the acrylate **4** (0.58 g, 5 mmol) in MeCN (25 mL) at room temperature. After three days, the mixture was filtered through Celite®, washed (3×25 mL EtOAc) and concentrated under reduced pressure. Purification by silica gel column chromatography (petrol/EtOAc, gradient from 20–100% EtOAc) followed by recrystallisation from petrol/Et_2O gave the alcohol **7** (1.05 g, 55% yield) as white needles. Mp 75.5–76.0 °C. R_f 0.6 (EtOAc); (Found: C, 60.3; H, 6.1; N, 3.6; S, 8.6. $C_{19}H_{23}NO_5S$ requires C, 60.5; H, 6.1; N, 3.7; S, 8.5); ν_{max} (film)/cm^{-1} 3520 br, 1733 and 1337; δ_H (500 MHz, $CDCl_3$) 2.28 (1H, ddt, *J* 10.1, 5.0 and 3.5, CH), 2.49 (3H, s, $SO_2C_6H_4CH_3$), 2.66 (1H, t, *J* 7.1, CH_2OH), 3.19 (1H, dd, *J* 15.0 and 5.1, $CHCH_AH_BN$), 3.64 (3H, s, CO_2CH_3), 3.72 (1H, dd, *J* 15.0 and 10.5, $CHCH_AH_BN$), 3.76–3.87 (2H, m, CH_2OH), 4.02 (1H, d, *J* 14.4, NCH_AH_BPh), 4.61 (1H, d, *J* 14.4, NCH_AH_BPh), 7.29 (2H, dd, *J* 6.9 and 2.6, Ar), 7.32–7.36 (3H, m, Ar), 7.38 (2H, d, *J* 8.0, Ar) and 7.77 (2H, d, *J* 8.3, Ar); δ_C (126 MHz, $CDCl_3$) 21.8, 46.3, 46.7, 52.2, 54.6, 59.8, 127.5, 128.5, 128.8, 129.0, 130.2, 135.7, 136.1, 144.1 and 172.9; *m/z* (EI) 378 (MH^+, 2%) and 91 ($C_7H_7^+$, 100). Found MH^+ 378.1367. $C_{19}H_{24}NO_5S$ requires 378.1375.

*4.1.3.14. Methyl 2-{[N-benzyl-(p-tolylsulfonyl)-amino]-methyl}-3-iodo-propanoate **9***. Following the *iodination procedure*, alcohol **7** (3.98 g, 10.5 mmol) gave, after purification by silica gel column chromatography (petrol/EtOAc, gradient from

petrol to 50% EtOAc) and recrystallisation from petrol/Et_2O, the alkyl iodide **9** (4.35 g, 85%) as white needles. Mp 84.5–85 °C. R_f 0.8 (petrol/EtOAc, 1:1); (Found: C, 47.0; H, 4.5; N, 2.7; I, 26.2; S, 7.0. $C_{19}H_{22}INO_4S$ requires C, 46.8; H, 4.6; N, 2.9; I, 26.2; S, 6.6); ν_{max} (film)/cm^{-1} 3030, 1737 and 1342; δ_H (500 MHz, $CDCl_3$) 2.49 (3H, s, $SO_2C_6H_4CH_3$), 2.88–2.93 (1H, m, CH), 3.18 (1H, dd, *J* 10.1 and 6.9, $CHCH_AH_BN$), 3.26 (1H, dd, *J* 10.1 and 4.7, $CHCH_AH_BN$), 3.30–3.40 (2H, m, CH_2I), 3.66 (3H, s, CO_2CH_3), 4.26 (1H, d, *J* 14.7, NCH_AH_BPh), 4.40 (1H, d, *J* 14.7, NCH_AH_BPh), 7.29 (2H, dd, *J* 6.9 and 2.6, Ar) and 7.28–7.39 (7H, m, Ar); δ_C (126 MHz, $CDCl_3$) 2.3, 21.3, 47.0, 50.2, 51.2, 52.0, 127.1, 127.9, 128.3, 128.5, 129.6, 135.3, 135.4, 143.5 and 171.4; *m/z* (ES) 510 (MNa^+, 17%) and 488 (MH^+, 100); *m/z* (EI) found MH^+ 488.0374. $C_{19}H_{23}INO_4S$ requires 488.0393.

4.1.3.15. Methyl 2-{[N-benzyl-(p-tolylsulfonyl)-amino]-methyl}-3-phenyl-propanoate ***11a***. Following *procedure A*, alkyl iodide **9** (244 mg, 0.5 mmol) and iodobenzene (0.86 μL, 0.65 mmol) gave, after purification by silica gel column chromatography (petrol/EtOAc, gradient from petrol to 50% EtOAc) and recrystallisation from petrol/Et_2O, the β^2-amino acid derivative **11a** (160 mg, 75%) as colourless blocks, which were analysed by X-ray crystallography. Mp 112–112.5 °C. R_f 0.5 (petrol/EtOAc, 1:1); ν_{max} (film)/cm^{-1} 3029, 1735 and 1340; δ_H (500 MHz, $CDCl_3$) 2.47 (3H, s, $SO_2C_6H_4CH_3$), 2.69 (1H, dd, *J* 13.8 and 6.8, $CHCH_AH_BPh$), 2.75 (1H, dd, *J* 13.8 and 8.6, $CHCH_AH_BPh$), 2.86–2.93 (1H, m, CH), 3.30 (1H, dd, *J* 14.4 and 6.2, $CHCH_AH_BN$), 3.35 (1H, dd, *J* 14.4 and 7.9, $CHCH_AH_BN$), 3.47 (3H, s, CO_2CH_3), 4.21 (1H, d, *J* 14.9, NCH_AH_BPh), 4.43 (1H, d, *J* 14.9, NCH_AH_BPh), 6.94 (2H, d, *J* 6.6, Ar), 7.19–7.35 (10H, m, Ar) and 7.68 (2H, d, *J* 8.3, Ar); δ_C (126 MHz, $CDCl_3$) 21.5, 36.2, 47.0, 50.2, 51.6, 53.5, 126.4, 127.3, 127.9, 128.3, 128.5, 128.6, 128.7, 129.7, 136.0, 136.1, 138.1, 143.4 and 174.0; *m/z* (EI) 438 (MH^+, 18%), 488 (M^+, 46) and 406 (M^+–MeO, 100). Found M^+ 437.1658. $C_{25}H_{27}NO_4S$ requires 437.1661.

In addition, following *procedure A*, alkyl iodide **9** (244 mg, 0.5 mmol) and bromobenzene (68.5 μg, 0.65 mmol) gave, after purification as previously described, the β^2-amino acid derivative **11a** (167 mg, 76%) as pale orange needles, spectroscopically consistent with that previously reported herein.

4.1.3.16. Methyl 2-{[N-benzyl-(p-tolylsulfonyl)-amino]-methyl}-3-(p-methoxyphenyl)-propanoate ***11b***. Following *procedure A*, alkyl iodide **9** (244 mg, 0.5 mmol) and 4-iodoanisole (152 mg, 0.65 mmol) gave, after purification by silica gel column chromatography (petrol/EtOAc, gradient from petrol to 50% EtOAc) and recrystallisation from heptane/EtOAc, the β^2-amino acid derivative **11b** (208 mg, 89%) as a pale grey solid. Mp 69–70.5 °C. R_f 0.55 (petrol/EtOAc, 1:1); (Found: C, 66.8; H, 6.1; N, 2.8; S, 6.6. $C_{26}H_{29}NO_5S$ requires C, 66.8; H, 6.3; N, 3.0; S, 6.9); ν_{max} (film)/cm^{-1} 2921, 1735 and 1341; δ_H (500 MHz, $CDCl_3$) 2.47 (3H, s, $SO_2C_6H_4CH_3$), 2.63 (1H, dd, *J* 13.9 and 6.7, $CHCH_AH_BAr$), 2.69 (1H, dd, *J* 13.9 and 6.6, $CHCH_AH_BAr$), 2.84 (1H, dq, *J* 7.9 and 6.6, CH), 3.29 (1H, dd, *J* 14.4 and 6.2, $CHCH_AH_BN$), 3.33 (1H, dd, *J* 14.4 and 7.9, $CHCH_AH_BN$), 3.47 (3H, s, CO_2CH_3), 3.81 (3H, s, $ArOCH_3$), 4.21 (1H, d, *J* 14.9, NCH_AH_BPh), 4.42 (1H, d, *J* 14.9, NCH_AH_BPh), 6.75–6.80 (2H, m, Ar), 6.83–6.87 (2H, m, Ar), 7.68 (2H, d, *J* 8.3, Ar) and 7.21–7.40 (7H, m, Ar); δ_C (126 MHz, $CDCl_3$) 21.6, 35.4, 47.3, 50.2, 51.7, 53.5, 55.2, 113.8, 127.4, 127.9, 128.5, 128.6, 129.2, 129.8, 130.2, 136.1, 136.2, 143.5, 158.2 and 174.2; *m/z* (EI) 467 (M^+, 13%) and 91 ($C_6H_7^+$, 100). Found M^+ 467.1774. $C_{26}H_{29}NO_5S$ requires 467.1766.

4.1.3.17. Methyl 2-{[N-benzyl-(p-tolylsulfonyl)-amino]-methyl}-3-(p-nitrophenyl)-propanoate ***11c***. Following *procedure A*, alkyl iodide **9** (244 mg, 0.5 mmol) and 1-iodo-4-nitro benzene (162 mg, 0.65 mmol) gave, after purification by silica gel column chromatography (petrol/EtOAc, gradient from petrol to 80% EtOAc) and recrystallisation from petrol/Et_2O, the β^2-amino acid derivative **11c** (145 mg, 60%) as a pale orange solid. Mp 68.5–69 °C. R_f 0.30 (petrol/EtOAc, 1:1); (Found: C, 62.1; H, 5.4; N, 5.6; S, 6.7. $C_{25}H_{26}N_2O_6S$ requires C, 62.2; H, 5.4; N, 5.8; S, 6.7); ν_{max} (film)/cm^{-1} 1735, 1519 and 1345 s; δ_H (500 MHz, $CDCl_3$) 2.49 (3H, s, $SO_2C_6H_4CH_3$), 2.74–2.82 (2H, m, $CHCH_AH_BAr$), 2.87–2.91, (1H, m, $CHCH_AH_BAr$), 3.27 (1H, dd, *J* 14.3 and 5.7, $CHCH_AH_BN$), 3.44 (1H, dd, *J* 14.3 and 7.2, $CHCH_AH_BN$), 3.48 (3H, s, CO_2CH_3), 4.09 (1H, d, *J* 14.7, NCH_AH_BPh), 4.53 (1H, d, *J* 14.7, NCH_AH_BPh), 6.98 (2H, d, *J* 8.7, Ar), 7.31–7.47 (7H, m, Ar), 7.75 (2H, d, *J* 8.3, Ar) and 8.05 (2H, d, *J* 8.7, Ar); δ_C (126 MHz, $CDCl_3$) 21.6, 35.5, 46.8, 51.0, 51.1, 54.3, 123.5, 127.4, 128.2, 128.7, 128.9, 129.6, 129.9, 135.7, 136.3, 143.9, 146.5, 146.6 and 173.2; *m/z* (EI) 483 (MH^+, 4%) and 91 ($C_6H_7^+$, 100). Found MH^+ 483.1594. $C_{25}H_{27}N_2O_6S$ requires 483.1590.

4.1.3.18. Methyl 2-{[N-benzyl-(p-tolylsulfonyl)-amino]-methyl}-3-(m-nitrophenyl)-propanoate ***11d***. Following *procedure A*, alkyl iodide **9** (244 mg, 0.5 mmol) and 1-iodo-3-nitro benzene (162 mg, 0.65 mmol) gave, after purification by silica gel column chromatography (petrol/EtOAc, gradient from petrol to 80% EtOAc) and recrystallisation from petrol/Et_2O, the β^2-amino acid derivative **11d** (130 mg, 54%) as a pale orange solid. Mp 114.5–116 °C. R_f 0.30 (petrol/EtOAc, 1:1); ν_{max} (film)/cm^{-1} 1735, 1528 and 1351 s; δ_H (500 MHz, $CDCl_3$) 2.49 (3H, s, $SO_2C_6H_4CH_3$), 2.68–2.75 (1H, m, CH), 2.80 (1H, dd, *J* 13.7 and 9.9, $CHCH_AH_BAr$), 2.90 (1H, dd, *J* 13.7 and 6.4, $CHCH_AH_BAr$), 3.28 (1H, dd, *J* 14.2 and 6.4, $CHCH_AH_BN$), 3.45 (1H, dd, *J* 14.3 and 7.8, $CHCH_AH_BN$), 3.49 (3H, s, CO_2CH_3), 4.10 (1H, d, *J* 14.6, NCH_AH_BPh), 4.55 (1H, d, *J* 14.6, NCH_AH_BPh), 7.23 (1H, d, *J* 7.7, Ar), 7.35–7.42 (8H, m, Ar), 7.67–7.69 (1H, m, Ar), 7.73–7.77 (2H, m, Ar) and 8.00–8.04 (1H, m, Ar); δ_C (126 MHz, $CDCl_3$) 21.6, 35.3, 46.9, 50.1, 51.9, 54.3, 121.6, 122.1, 123.3, 123.5, 127.4, 128.4, 128.7, 128.9, 129.2, 129.9, 130.3, 133.1, 135.2, 135.8, 136.1, 140.6, 143.8, 148.2 and 173.2; *m/z* (EI) 483 (MH^+, 8%) and 91 ($C_6H_7^+$, 100). Found MH^+ 483.1569. $C_{25}H_{27}N_2O_6S$ requires 483.1590.

*4.1.3.19. Methyl 2-{[N-benzyl-(p-tolylsulfonyl)-amino]-methyl}-3-(p-hydroxyphenyl)-propanoate **11e***. Following *procedure A*, alkyl iodide **9** (244 mg, 0.5 mmol) and 4-iodophenol (143 mg, 0.65 mmol) gave, after purification by silica gel column chromatography (petrol/EtOAc, gradient from petrol to 70% EtOAc) and recrystallisation from petrol/Et_2O, the β^2-amino acid derivative **11e** (141 mg, 62%) as a pale orange solid. Mp 163.5–164 °C. R_f 0.40 (petrol/EtOAc, 1:1); (Found: C, 65.8; H, 5.8; N, 2.7; S, 6.8. $C_{25}H_{27}NO_5S$ requires C, 66.2; H, 6.0; N, 3.1; S, 7.1); ν_{max} (film)/cm^{-1} 3416 br, 1732 and 1338; δ_H (500 MHz, $CDCl_3$) 2.37 (3H, s, $SO_2C_6H_4CH_3$), 2.51 (1H, dd, *J* 13.9 and 6.7, $CHCH_AH_BAr$), 2.56 (1H, dd, *J* 13.9 and 8.6, $CHCH_AH_BAr$), 2.69–2.78 (1H, m, CH), 3.18 (1H, dd, *J* 12.9 and 4.8, $CHCH_AH_BN$), 3.22 (1H, dd, *J* 12.9 and 6.3, $CHCH_AH_BN$), 3.36 (3H, s, CO_2CH_3), 4.10 (1H, d, *J* 14.9, NCH_AH_BPh), 4.31 (1H, d, *J* 14.9, NCH_AH_BPh), 4.70 (s, 1H, OH), 6.56–6.63 (2H, m, Ar), 6.67–6.71 (2H, m, Ar), 7.14–7.30 (7H, m, Ar) and 7.58 (2H, d, *J* 8.3, Ar); δ_C (126 MHz, $CDCl_3$) 21.6, 35.4, 47.3, 50.1, 51.7, 53.5, 115.2, 127.4, 127.9, 128.6, 128.7, 129.8, 129.9, 130.3, 136.1, 136.2, 143.5, 154.2 and 174.3; *m/z* (EI) 453 (M^+, 2%) and 91 (100%, $C_6H_7^+$). Found M^+ 453.1629. $C_{25}H_{27}NO_5S$ requires 453.1610.

*4.1.3.20. Methyl 2-{[N-benzyl-(p-tolylsulfonyl)-amino]-methyl}-3-(m-hydroxyphenyl)-propanoate **11f***. Following *procedure A*, alkyl iodide **9** (244 mg, 0.5 mmol) and 3-iodophenol (143 mg, 0.65 mmol) gave, after purification by silica gel column chromatography (petrol/EtOAc, gradient from petrol to 70% EtOAc), the β^2-amino acid derivative **11f** (142 mg, 62%) as an orange oil. R_f 0.30 (petrol/EtOAc, 1:1); ν_{max} (film)/cm^{-1} 3434 br, 2951 and 1732; δ_H (500 MHz, $CDCl_3$) 2.35 (3H, s, $SO_2C_6H_4CH_3$), 2.51 (1H, dd, *J* 13.8 and 6.7, $CHCH_AH_BAr$), 2.59 (1H, dd, *J* 13.9 and 8.6, $CHCH_AH_BAr$), 2.75–2.82 (1H, m, CH), 3.17 (1H, dd, *J* 14.4 and 6.3, $CHCH_AH_BN$), 3.23 (1H, dd, *J* 14.4 and 7.8, $CHCH_AH_BN$), 3.37 (3H, s, CO_2CH_3), 4.09 (1H, d, *J* 14.9, NCH_AH_BPh), 4.30 (1H, d, *J* 14.9, NCH_AH_BPh), 5.38 (s, 1H, OH), 6.30–6.32 (1H, m, Ar), 6.39 (1H, d, *J* 7.7, Ar), 6.59 (1H, ddd, *J* 8.1, 2.5 and 0.7, Ar), 6.98 (1H, t, *J* 7.8, Ar), 7.14–7.23 (7H, m, Ar) and 7.56 (2H, d, *J* 8.3, Ar); δ_C (126 MHz, $CDCl_3$) 21.6, 36.0, 46.9, 50.2, 51.8, 53.6, 113.6, 115.7, 121.0, 127.4, 127.9, 128.6, 128.7, 129.6, 129.8, 136.0, 136.1, 139.9, 143.6, 155.8 and 174.3; *m/z* (EI) 453 (M^+, 2%) and 91 ($C_6H_7^+$, 100). Found M^+ 453.1606. $C_{25}H_{27}NO_5S$ requires 453.1610.

*4.1.3.21. Methyl 2-[(N-benzyl-amino)-methyl]-3-phenyl-propanoate **13***. Using conditions originally reported for the cleavage of sulfonyl aziridines[26] and piperidines,[27] magnesium turnings (0.57 g, 22.9 mmol) were added to a stirred suspension of the sulfonyl-protected β^2-amino acid **11a** (200 mg, 0.46 mmol) in MeOH (10 mL) at room temperature. The reaction proceeded with a noticeable exotherm. After 1 h, the reaction was quenched (30 mL HCl, 2 M), basified (aqueous K_2CO_3) to pH 9 and extracted with EtOAc (3×30 mL). The combined organic fractions were washed (2×20 mL brine), dried ($MgSO_4$) and evaporated under reduced pressure and the crude product purified by silica gel column chromatography eluting with EtOAc to give the amine **13** (114 mg, 88% yield) as a colourless oil. R_f 0.3 (EtOAc); ν_{max} (film)/cm^{-1} 2949 and 1731; δ_H (500 MHz, $CDCl_3$) 2.80–2.99 (5H, m, NCH_2CHCH_2Ph), 3.68 (3H, s, CO_2CH_3), 3.78 (1H, d, *J* 13.3, NCH_AH_BPh), 3.83 (1H, d, *J* 13.3, NCH_AH_BPh) and 7.17–7.39 (10H, m, Ar); δ_C (126 MHz, $CDCl_3$) 36.3, 47.9, 50.2, 51.7, 53.7, 126.4, 126.9, 128.1, 128.4, 128.5, 128.7, 128.9, 139.0, 140.3 and 175.3; *m/z* (EI) 284 (MH^+, 6%), 283 (M^+, 12) and 91 ($C_6H_7^+$, 100). Found M^+ 283.1574. $C_{18}H_{21}NO_2$ requires 283.1572.

*4.1.3.22. N-Benzyl-2-[(benzyl-amino)-methyl]-3-hydroxy-propanamide **15***. Following the procedure reported to afford the corresponding β-lactam **14**,[19,20] benzylamine (0.50 mL, 4.55 mmol) was added dropwise to a stirred solution of the acrylate **4** (132 mg, 1.14 mmol) in dry MeOH (0.17 mL) at room temperature. After 30 min the reaction was heated at reflux for 16 h. Removal of the solvent under reduced pressure gave a crude solid, which was washed with hexane and then recrystallised (EtOAc/heptane) to give the amide **15** (149 mg, 44%) as colourless plates, which were analysed by X-ray crystallography. Mp 95–96.5 °C; ν_{max} (film)/cm^{-1} 3273, 3061 and 1660; δ_H (500 MHz, CD_3OD) 2.65–2.73 (1H, m, CH), 2.78 (1H, dd, *J* 12.0 and 5.2, $CHCH_AH_BN$), 2.88 (1H, dd, *J* 12.0 and 8.2, $CHCH_AH_BN$), 3.68 (1H, dd, *J* 10.7 and 6.1, $CH_2NHCH_AH_BPh$), 3.72–3.78 (3H, m, $CH_2NHCH_AH_BPh$ and $CHCH_2OH$), 4.41 (1H, d, *J* 15.0, $CONHCH_AH_BPh$), 4.36 (1H, d, *J* 15.0, $CONHCH_AH_BPh$) and 7.20–7.32 (10H, m, Ar); δ_C (126 MHz, CD_3OD) 44.1, 48.4, 49.9, 54.4, 63.4, 128.2, 128.3, 128.6, 129.4, 129.5, 129.6, 139.9, 140.3 and 175.5; *m/z* (EI) 299 (MH^+, 9%), 298 (M^+, 14), 106 ($BnNH_2^+$, 87) and 91 ($C_6H_7^+$, 100). Found MH^+ 299.1774. $C_{18}H_{23}N_2O_2$ requires 299.1760. The filtrate was concentrated under reduced pressure to afford the amino alcohol **5** (76 mg, 30%) as a pale yellow oil, spectroscopically consistent with that previously reported herein.

*4.1.3.23. 1-Benzyl-3-hydroxymethyl-azetidin-2-one **14***. Following a procedure reported for a closely related compound,[28] the amino alcohol **5** (1.78 g, 8 mmol) in dry THF (5 mL) was added dropwise to a stirred solution of *tert*-butyl magnesium chloride (24 mL, 24 mmol, 1 M solution in THF) under nitrogen. After 3 h the reaction was quenched with saturated aqueous NH_4Cl solution, extracted with EtOAc (3×30 mL) and the combined organic fractions were washed with brine (2×20 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Purification by silica gel column chromatography (CH_2Cl_2/MeOH, gradient from CH_2Cl_2 to 2.5% MeOH) gave the hydroxymethyl β-lactam **14** (1.02 g, 67% yield) as a pale yellow oil. R_f 0.2 (2.5% MeOH/CH_2Cl_2); ν_{max} (film)/cm^{-1} 3403, 2922 and 1729; δ_H (500 MHz, $CDCl_3$) 3.10 (1H, dd, *J* 5.5 and 2.5, $CHCH_AH_BN$), 3.15 (1H, app t, *J* 5.4, $CHCH_AH_BN$), 3.30 (1H, app qd, *J* 4.9 and 2.5, CH), 3.75 (1H, dd, *J* 11.7 and 4.4, CH_AH_BOH), 3.90 (1H, dd, *J* 11.7 and 4.9, CH_AH_BOH), 4.29 (1H, d, *J* 15.1, NCH_AH_BPh), 4.33 (1H, d, *J* 15.1, NCH_AH_BPh) and 7.13–7.29 (5H, m, Ar); δ_C (126 MHz, $CDCl_3$) 42.0, 45.9, 52.1, 59.3, 127.7, 128.1,

128.5, 128.6, 128.8, 135.4 and 168.9; *m/z* (ES) 214 (MNa^+, 60%) and 192 (MH^+, 55). Found MH^+ 192.1028. $C_{11}H_{14}NO_2$ requires 192.1025. Spectroscopic data is *not* consistent with that previously reported.[20]

4.1.3.24. 1-Benzyl-3-[(p-toluenesulfonyloxy)-methyl]-azetidin-2-one ***16***. Using the procedure previously described for tosylation of protected serine,[37] DMAP (3.8 mg, 0.03 mmol), Me_3NHCl (6.0 mg, 0.06 mmol) and *p*-toluenesulfonic acid (120 mg, 0.63 mmol) were added to a stirred solution of the hydroxymethyl β-lactam **14** (120 mg, 0.63 mmol) in CH_2Cl_2 (1.1 mL) at 0 °C. Triethylamine (88 μL, 0.63 mmol) in CH_2Cl_2 (0.27 mL) was added dropwise to the reaction mixture and the resulting slurry stirred for 2 h at 0 °C. The reaction mixture was diluted with water (20 mL), extracted with CH_2Cl_2 (3×15 mL) and the combined organic fractions washed with brine (2×10 mL), dried (Na_2SO_4) and evaporated under reduced pressure. Purification by silica gel column chromatography (petrol/EtOAc, gradient from petrol to 80% EtOAc) followed by recrystallisation from EtOAc/heptane gave the tosylate **16** (159 mg, 73%) as colourless blocks, which were analysed by X-ray crystallography. Mp 101–102.5 °C. R_f 0.4 (EtOAc); (Found: C, 62.9; H, 5.4; N, 3.9; S, 9.0. $C_{18}H_{19}NO_4S$ requires C, 62.6; H, 5.5; N, 4.1; S, 9.3); ν_{max} (film)/cm^{-1} 2923, 1749, 1176 and 1360 s; δ_H (500 MHz, $CDCl_3$) 2.38 (3H, s, $SO_2C_6H_4CH_3$), 3.05 (1H, dd, *J* 5.9 and 2.5, $CHCH_AH_BN$), 3.12–3.27 (1H, m, $CHCH_AH_BN$), 3.35–3.46 (1H, m, CH), 4.16 (1H, dd, *J* 10.6 and 6.8, CH_AH_BOTs), 4.20–4.29 (2H, m, CH_AH_BOTs and NCH_AH_BPh), 4.36 (1H, d, *J* 15.1, NCH_AH_BPh), 7.08–7.34 (7H, m, Ar) and 8.34 (2H, d, *J* 8.3, Ar); δ_C (126 MHz, $CDCl_3$) 21.7, 42.5, 46.1, 49.1, 66.6, 127.9, 128.0, 128.1, 128.9, 129.9, 132.4, 134.9, 145.2 and 165.3; *m/z* (ES) 368 (MNa^+, 28%) and 346 (MH^+, 100). Found MH^+ 346.1112. $C_{18}H_{20}NO_4S$ requires 346.1113.

4.1.3.25. 1-Benzyl-3-iodomethyl-azetidin-2-one ***17***. Following the *iodination procedure*, hydroxymethyl β-lactam **14** (2.01 g, 10.5 mmol) gave, after purification by silica gel column chromatography (petrol/EtOAc, gradient from petrol to 80% EtOAc), the alkyl iodide **17** (2.40 g, 76%) as a colourless oil. R_f 0.3 (petrol/EtOAc, 1:1); ν_{max} (film)/cm^{-1} 2922 and 1748; δ_H (500 MHz, $CDCl_3$) 2.97 (1H, dd, *J* 2.2 and 5.9, $CHCH_AH_BN$), 3.30–3.34 (1H, m, $CHCH_AH_BN$), 3.35 (1H, dd, *J* 10.1 and 1.5, CH_AH_BI), 3.51 (1H, dd, *J* 10.1 and 3.1, CH_AH_BI), 3.52–3.55 (1H, m, CH), 4.39 (1H, d, *J* 14.9, NCH_AH_BPh), 4.45 (1H, d, *J* 14.9, NCH_AH_BPh) and 7.27–7.41 (5H, m, Ar); δ_C (126 MHz, $CDCl_3$) 0.0, 44.9, 45.5, 50.8, 126.7, 127.2, 127.7, 133.9 and 165.5; *m/z* (ES) 324 (MNa^+, 27%) and 302 (MH^+, 100); *m/z* (EI) Found MH^+ 302.0031. $C_{11}H_{13}INO$ requires 302.0042.

The alkyl iodide **17** was also prepared using a procedure previously described for a tosylated serine derivative.[37] Sodium iodide (50 mg, 0.33 mmol) was added to a stirred solution of the tosylate **16** (57 mg, 0.165 mmol) in acetone (2 mL) at room temperature and was stirred in the dark for 24 h, after which time another equivalent of sodium iodide (25 mg, 0.16 mmol) was added. Stirring was continued for a further 24 h before the reaction mixture was diluted with water (10 mL), extracted with EtOAc (3×15 mL) and the combined organic fractions washed with aqueous sodium thiosulfate solution (2×10 mL, 1 M) and brine, dried ($MgSO_4$) and concentrated under reduced pressure. Purification by silica gel column chromatography (petrol/EtOAc, gradient from petrol to 50% EtOAc) gave the alkyl iodide **17** (44 mg, 89%) as a colourless oil, spectroscopically consistent with that previously reported herein.

4.1.3.26. 1,3-Dibenzyl-azetidin-2-one ***18a***. Following *procedure A*, alkyl iodide **17** (151 mg, 0.5 mmol) and iodobenzene (0.86 μL, 0.65 mmol) gave, after purification by silica gel column chromatography (petrol/EtOAc, gradient from petrol to 80% EtOAc) and recrystallisation from heptane/EtOAc, the β^2-amino acid derivative **18a** (90 mg, 72%) as pale orange needles. Mp 49.5–51 °C. R_f 0.2 (50% EtOAc/petrol); (Found: C, 81.1; H, 6.9; N, 5.6. $C_{17}H_{17}NO$ requires C, 81.2; H, 6.8; N, 5.6); ν_{max} (film)/cm^{-1} 3029 and 1746; δ_H (500 MHz, $CDCl_3$) 2.79 (1H, dd, *J* 5.7 and 2.4, $CHCH_AH_BN$), 2.86 (1H, dd, *J* 14.4 and 8.4, $CHCH_AH_BPh$), 3.00 (1H, dd, *J* 14.4 and 4.9, $CHCH_AH_BPh$), 3.07 (1H, t, *J* 5.4, $CHCH_AH_BN$), 3.38–3.43 (1H, m, CH), 4.10 (1H, d, *J* 15.2, NCH_AH_BPh), 4.34 (1H, d, *J* 15.2, NCH_AH_BPh), 6.91 (2H, dd, *J* 7.6 and 1.7, Ar) and 7.09–7.21 (8H, m, Ar); δ_C (126 MHz, $CDCl_3$) 34.2, 43.9, 45.7, 50.7, 126.6, 127.6, 127.9, 128.6, 128.8, 129.0, 135.5, 138.1 and 169.7; *m/z* (ES) 274 (MNa^+, 6%) and 252 (MH^+, 100). Found MH^+ 252.1392. $C_{17}H_{18}NO$ requires 252.1388.

Following *procedure A*, alkyl iodide **17** (217 mg, 0.5 mmol) and bromobenzene (68.5 μg, 0.65 mmol) gave, after purification as previously described, the β-lactam **18a** (86 mg, 68%) as pale orange needles, spectroscopically consistent with that previously reported herein.

4.1.3.27. 1-Benzyl-3-(p-methoxybenzyl)-azetidin-2-one ***18b***. Following *procedure A*, alkyl iodide **17** (151 mg, 0.5 mmol) and 4-iodoanisole (152 mg, 0.65 mmol) gave, after purification by silica gel column chromatography (petrol/EtOAc, gradient from petrol to 80% EtOAc), the β^2-amino acid derivative **18b** (90 mg, 65% yield) as a pale orange oil. R_f 0.4 (50% EtOAc/petrol); ν_{max} (film)/cm^{-1} 2910 and 1745; δ_H (500 MHz, $CDCl_3$) 2.86 (1H, dd, *J* 5.6 and 2.4, $CHCH_AH_BN$), 2.92 (1H, dd, *J* 14.5 and 7.8, $CHCH_AH_BAr$), 2.99 (1H, dd, *J* 14.5 and 5.0, $CHCH_AH_BAr$), 3.15 (1H, t, *J* 5.4, $CHCH_AH_BN$), 3.46 (1H, dtd, *J* 7.5, 5.0 and 2.4, CH), 3.79 (3H, s, $ArOCH_3$), 4.14 (1H, d, *J* 15.2, NCH_AH_BPh), 4.45 (1H, d, *J* 15.2, NCH_AH_BPh), 6.73–6.88 (2H, m, Ar), 6.93–7.02 (2H, m, Ar), 7.06–7.16 (2H, m, Ar) and 7.22–7.26 (3H, m, Ar); δ_C (126 MHz, $CDCl_3$) 33.2, 43.7, 45.7, 50.9, 55.3, 113.9, 127.5, 127.9, 128.7, 129.8, 130.2, 135.4, 158.4 and 169.8; *m/z* (ES) 282 (MH^+, 100%). Found MH^+ 282.1502. $C_{18}H_{20}NO_2$ requires 282.1494.

4.1.3.28. 1-Benzyl-3-(p-nitrobenzyl)-azetidin-2-one ***18c***. Following *procedure A*, alkyl iodide **17** (151 mg, 0.5 mmol) and 1-iodo-4-nitro benzene (162 mg, 0.65 mmol) gave, after

purification by silica gel column chromatography (petrol/EtOAc, gradient from petrol to 100% EtOAc), the β-lactam **18c** (65 mg, 44%) as a pale orange oil. R_f 0.30 (petrol/EtOAc, 1:1); ν_{max} (film)/cm^{-1} 2898, 1746, 1518 and 1346 s; δ_H (500 MHz, $CDCl_3$) 2.76 (1H, dd, *J* 5.8 and 2.4, CHCH_AH$_B$N), 3.01 (1H, dd, *J* 14.5 and 7.4, CHCH_AH$_B$Ar), 3.07 (1H, dd, *J* 14.5 and 5.8, CHCH$_A$$H_B$Ar), 3.17 (1H, app t, *J* 5.5, CHCH$_A$$H_B$N), 3.41–3.51 (1H, m, CH), 4.09 (1H, d, *J* 15.0, NCH_AH$_B$Ph), 4.35 (1H, d, *J* 15.0, NCH$_A$$H_B$Ph), 6.94–6.97 (2H, m, Ar), 7.16–7.20 (3H, m, Ar), 7.28–7.31 (2H, m, Ar) and 8.02–8.05 (2H, m, Ar); δ_C (126 MHz, $CDCl_3$) 33.9, 43.5, 45.8, 49.7, 123.6, 127.7, 127.9, 128.7, 129.9, 135.1, 145.5, 146.8 and 168.6; *m/z* (ES) 319 (MNa$^+$, 4%) and 297 (MH$^+$, 100). Found MH$^+$ 297.1232. $C_{17}H_{17}N_2O_3$ requires 297.1239.

4.1.3.29. 1-Benzyl-3-(m-nitrobenzyl)-azetidin-2-one ***18d***. Following *procedure A*, alkyl iodide **17** (151 mg, 0.5 mmol) and 1-iodo-3-nitro benzene (162 mg, 0.65 mmol) gave, after purification by silica gel column chromatography (petrol/EtOAc, gradient from petrol to 100% EtOAc), the β-lactam **18d** (70 mg, 47%) as a pale orange oil. R_f 0.35 (50% EtOAc/petrol); ν_{max} (film)/cm^{-1} 2918, 1743, 1527 and 1351 s; δ_H (500 MHz, $CDCl_3$) 2.80 (1H, dd, *J* 5.8 and 2.4, CHCH_AH$_B$N), 3.01 (1H, dd, *J* 14.6 and 7.8, CHCH_AH$_B$Ar), 3.10 (1H, dd, *J* 14.6 and 5.6, CHCH$_A$$H_B$Ar), 3.15–3.23 (1H, m, CHCH$_A$$H_B$N), 3.40–3.55 (1H, m, CH), 4.13 (1H, d, *J* 15.0, NCH_AH$_B$Ph), 4.35 (1H, d, *J* 15.0, NCH$_A$$H_B$Ph), 6.96–6.98 (2H, m, Ar), 7.18–7.21 (3H, m, Ar), 7.37–7.41 (1H, m, Ar), 7.52–7.54 (1H, m, Ar) and 8.00–8.03 (2H, m, Ar); δ_C (126 MHz, $CDCl_3$) 34.3, 44.1, 46.3, 50.4, 122.3, 124.2, 128.2, 128.4, 129.2, 129.9, 135.6, 135.9, 140.4, 148.7 and 169.1; *m/z* (ES) 297 (MH$^+$, 100%). Found MH$^+$ 297.1248. $C_{17}H_{17}N_2O_3$ requires 297.1239.

4.1.3.30. 1-Benzyl-3-(p-hydroxybenzyl)-azetidin-2-one ***18e***. Following *procedure A*, alkyl iodide **17** (151 mg, 0.5 mmol) and 4-iodophenol (143 mg, 0.65 mmol) gave, after purification by silica gel column chromatography (petrol/EtOAc, gradient from petrol to 100% EtOAc) and recrystallisation from pentane/EtOAc, the β^2-amino acid derivative **18e** (75 mg, 56%) as a pale orange solid. Mp 170–171.5 °C. R_f 0.15 (40% EtOAc/petrol); ν_{max} (film)/cm^{-1} 3262 br, 2922 and 1722; δ_H (500 MHz, CD_3OD) 2.86 (1H, dd, *J* 14.4 and 5.1, CHCH_AH$_B$Ar), 2.89–2.94 (2H, m, CHCH$_A$$H_BAr, CHCH_AH_B$N), 3.21 (1H, t, *J* 5.4, CHCH$_A$$H_B$N), 3.39–3.64 (1H, m, CH), 4.09 (1H, d, *J* 15.3, NCH_AH$_B$Ph), 4.46 (1H, d, *J* 15.2, NCH$_A$$H_B$Ph), 6.69–6.71 (2H, m, Ar), 6.88–6.90 (2H, m, Ar), 7.08–7.10 (2H, m, Ar) and 7.15–7.20 (3H, m, Ar); δ_C (126 MHz, CD_3OD) 33.6, 44.3, 46.4, 51.6, 116.3, 128.4, 128.7, 129.3, 129.7, 131.6, 136.7, 157.4 and 172.6; *m/z* (EI) 268 (MH$^+$, 5%) and 267 (M$^+$, 27). Found M$^+$ 267.1262. $C_{17}H_{17}NO_2$ requires 267.1259.

4.1.3.31. 1-Benzyl-3-(m-hydroxybenzyl)-azetidin-2-one ***18f***. Following *procedure A*, alkyl iodide **17** (151 mg, 0.5 mmol) and 3-iodophenol (143 mg, 0.65 mmol) gave, after purification by silica gel column chromatography (petrol/EtOAc, gradient from petrol to 100% EtOAc) and recrystallisation from heptane/EtOAc, the β^2-amino acid derivative **18f** (70 mg, 52%) as pale orange needles. Mp 145.5–147.0 °C. R_f 0.20 (40% EtOAc/petrol); ν_{max} (film)/cm^{-1} 3289 br and 1722; δ_H (500 MHz, $CDCl_3$) 2.81–2.86 (2H, m, CHCH_AH$_B$N, CHCH_AH$_B$Ar), 2.91 (1H, dd, *J* 14.4 and 5.1, CHCH$_A$$H_B$Ar), 3.09 (1H, t, *J* 5.4, CHCH$_A$$H_B$N), 3.22–3.59 (1H, m, CH), 4.09 (1H, d, *J* 15.2, NCH_AH$_B$Ph), 4.36 (1H, d, *J* 15.2, NCH$_A$$H_B$Ph), 6.59 (1H, d, *J* 7.6, Ar), 6.65–6.76 (2H, m, Ar), 6.88–6.95 (3H, m, Ar), 7.04 (1H, t, *J* 7.8, Ar) and 7.15–7.20 (2H, m, Ar); δ_C (126 MHz, $CDCl_3$) 33.8, 43.9, 45.9, 50.3, 113.9, 116.1, 121.0, 127.6, 127.9, 128.8, 129.7, 135.1, 139.3, 156.5 and 170.4; *m/z* (ES) 290 (MNa$^+$, 78%) and 268 (MH$^+$, 100). Found MH$^+$ 268.1346. $C_{17}H_{18}NO_2$ requires 268.1338.

5. X-ray crystallography

Crystallographic data were collected and measured on a Bruker Smart CCD area detector with an Oxford Cryosystems low temperature system at T=150(2) K.

Crystal data for **11a**: $C_{25}H_{27}NO_4S$, M=437.54, monoclinic, a=17.1018(14), b=5.8145(4), c=22.6997(17) Å, β=98.521(5)°, U=2232.3(3) Å^3, space group Cc, Z=4, μ(Mo Kα)=0.177 mm^{-1}, 19,770 reflections collected, 4960 independent (R=0.0443). Final R indices [$I>2\sigma(I)$] R=0.0384, wR_2=0.0777. R indices (all data) R=0.0458, wR_2=0.0815. Absolute structure parameter −0.01(6).

Crystal data for **15**: $C_{18}H_{22}N_2O_2$, M=298.38, monoclinic, a=15.2861(19), b=5.6781(7), c=18.199(6) Å, β=98.893(8)°, U=1560.6(3) Å^3, space group $P2_1/c$, Z=4, μ(Mo Kα)=0.083 mm^{-1}, 9664 reflections collected, 2668 independent (R=0.0914). Final R indices [$I>2\sigma(I)$] R=0.0675, wR_2=0.1639. R indices (all data) R=0.0954, wR_2=0.1862.

Crystal data for **16**: $C_{18}H_{19}NO_4S$, M=345.40, monoclinic, a=18.9157(14), b=7.7269(6), c=11.4895(9) Å, β=97.736(8)°, U=1664.0(2) Å^3, space group $P2_1/c$, Z=4, μ(Mo Kα)=0.216 mm^{-1}, 21,270 reflections collected, 3887 independent (R=0.0651). Final R indices [$I>2\sigma(I)$] R=0.0410, wR_2=0.0806. R indices (all data) R=0.0737, wR_2=0.0988.

Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC 669758–669760, respectively. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 (0)1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).

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References and notes

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