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β^3-Amino acids by nucleophilic ring-opening of *N*-nosyl aziridines

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Abstract—*N*-Nosyl aziridines can be easily prepared from 1,2-amino alcohols derived from α-amino acids. Nucleophilic ring-opening of *N*-nosyl aziridines with cyanide ions followed by hydrolysis of the corresponding nitriles lead to *N*-nosyl β^3-amino acids, which can be readily converted into a variety of derivatives bearing adequate functionality for peptide synthesis. The proposed methodology is simple, efficient, and amenable to large-scale preparations.

1. Introduction

Despite being less abundant than their α analogues, β-amino acids are present in nature as components of a vast array of metabolites[1] and have been considered precursors of β-lactam antibiotics.[2] They are also building blocks of β-peptides, which have recently attracted much attention owing to their ability to fold into defined three-dimensional structures.[3,4] Thus, it is not surprising that development of new synthetic pathways to gain access to enantiomerically pure β-amino acids is nowadays an area of active research.[5–7] In this context, we have recently disclosed a synthesis of a *N*,*N*-disubstituted cyclo-β^3-tetrapeptide derived from β-homophenylalanine which has been identified as a potential molecular scaffold suitable for combinatorial chemistry[8] and, therefore, it was crucial to be provided with a large supply of the aforementioned β^3-amino acid.[9] Taking into account that homologation of the parent α-amino acids is one of the most powerful strategies for this purpose,[5,6] we envisioned that the use of *N*-(*p*-nitrobenzenesulfonyl)aziridines, readily available from α-amino acids, might constitute a convenient approach to the synthesis of β^3-amino acids and their *N*-alkyl derivatives, assuming that the strong electron-withdrawing *p*-nitrobenzenesulfonyl group (Ns, nosyl) should facilitate (i) the nucleophilic ring-opening of the aziridine, (ii) the subsequent *N*-alkylation reaction, and (iii) its final removal. According to these ideas, we herein disclose a convenient and highly efficient methodology to transform α-amino acids into their β^3-counterparts using *N*-nosyl aziridines as key intermediates.[8,10] Such a strategy allows access to *N*-alkyl and/or *N*-protected β^3-amino acids in a straightforward manner.

Keywords: amino acids and derivatives; aziridines; homologation; sulfonamides.

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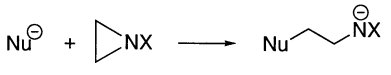
2. Results and discussion

It is well known that although ring strain renders aziridines susceptible to ring-opening reactions, extremely strong nucleophiles or acid catalysis are required in the case of non-activated aziridines (X=H, alkyl, or aryl in Scheme 1). Therefore, it becomes imperative to introduce substituents which can stabilize the negative charge on the nitrogen atom (X=COR, CO_2R, SO_2R) to increase the reactivity of aziridine rings towards nucleophiles.[11]

The *p*-toluenesulfonyl group (X=Ts) is probably the prototype of this kind of substituent and several strategies for the preparation of enantiomerically pure *N*-(*p*-toluenesulfonyl)-aziridines have been already reported.[12] Unfortunately, later removal of the tosyl group is often troublesome and requires long reaction times and the use of harsh reductive conditions.[13] Therefore, other more easily removable sulfonamido groups, like the strong electron-withdrawing nosyl group, may be considered as synthetic equivalents of the tosyl group and preferred for its easier manipulation in the deprotection step.[14] We have found that such *N*-nosyl aziridines can be easily prepared in one-pot procedure using 1,2-amino alcohols as starting materials which, in turn, are commercially available or readily accessible from natural α-amino acids in enantiomerically pure form.[15] Subsequent nucleophilic ring-opening of these aziridines with cyanide ions, followed by hydrolysis of the intermediate nitriles, lead to the target *N*-nosyl β^3-amino acids in good yields (see Scheme 2 and Table 1).

As shown in Scheme 2, a variety of *N*-nosyl β^3-amino acids were prepared from 1,2-amino alcohols **1** according to this



Scheme 1.

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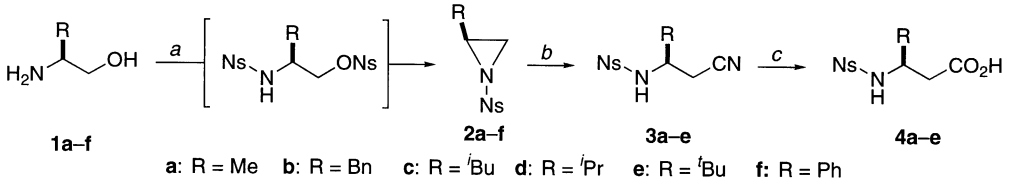


Scheme 2. (a) NsCl, CH_2Cl_2/pyridine, 2–4 h, then 2 M KOH; (b) NaCN, CH_3CN/H_2O, 24 h; (c) conc. HCl/HOAc, reflux, 4 h.

Table 1. Preparation of *N*-nosyl β^3-amino acids from 1,2-amino alcohols

	R	Amino alcohol	Amino acid	Yield[a] (%)
1	Me	**1a**	**4a**	75
2	Bn	**1b**	**4b**	65
3	^{i}Bu	**1c**	**4c**	60
4	^{i}Pr	**1d**	**4d**	60
5	*t*-Bu	**1e**	**4e**	60

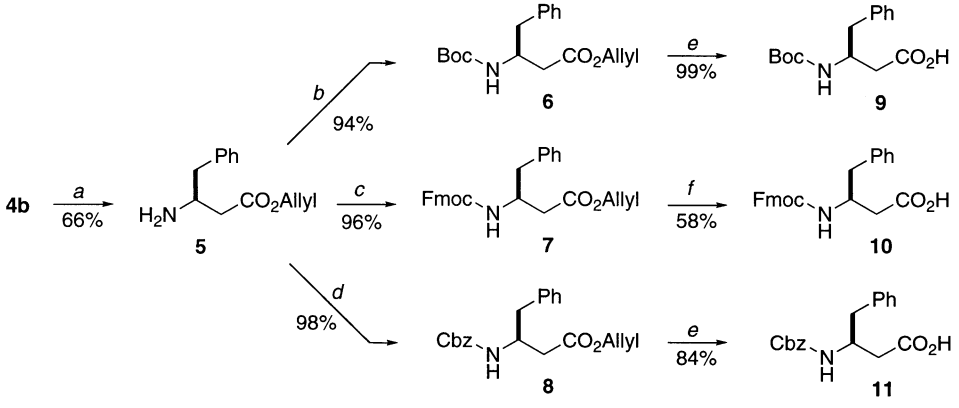
[a] Overall yield of pure **4** from **1**.

strategy. Preparation of aziridines **2** was initially troublesome because reaction of **1** with 2.2 equiv. of *p*-nitrophenylsulfonyl chloride (NsCl) in pyridine was not complete, even at 100°C; longer reaction times led to undesirable decompositions and all our attempts to isolate the corresponding dinosylated amino alcohols resulted in low yields. Finally, reaction of **1** with an excess of NsCl (3 equiv.) in CH_2Cl_2/pyridine at rt for 2–4 h, followed by treatment with aqueous 2 M KOH smoothly afforded **2**. This experimental procedure is highly appealing because the reaction can be run in one-pot at multi-gram scale and gives in excellent yields (>90%) the corresponding *N*-nosyl aziridines, which can be used in the next step without further purification.

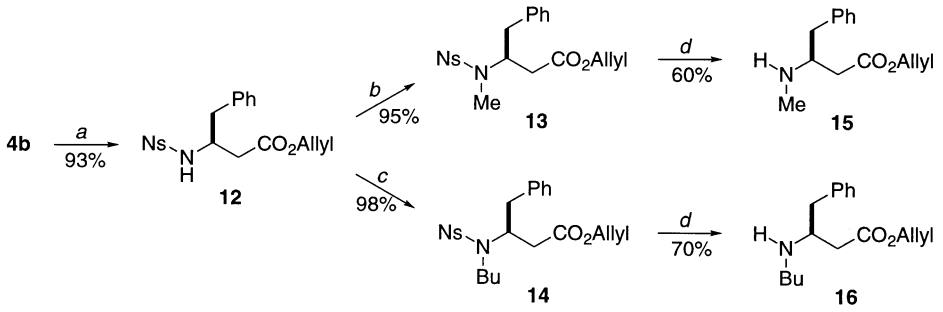
Having in hand the desired *N*-nosyl aziridines we next evaluated their nucleophilic ring-opening process promoted by cyanide ions. After a careful optimization, it was found that simple stirring of a mixture of crude *N*-nosyl aziridines **2** and NaCN in CH_3CN/H_2O[16] afforded in high yields (70–88% from **1**) the desired *N*-nosyl β-amino nitriles **3** that, once again, could be used in the next step without further purification. According to NMR spectra of **3**, the aforementioned conditions produced a regioselective ring-opening of the heterocycle except for phenyl aziridine **2f**, which gave a complex mixture probably as a consequence of the additional activation introduced by the phenyl group.

Hydrolysis of the *N*-nosyl β-amino nitriles proved to be strongly dependent on their structure. For instance, heating of **3b** and **3e** in conc. HCl at reflux for 15 h gave on cooling the corresponding *N*-nosyl β^3-amino acids **4b** and **4e** as highly pure crystalline products in 92 and 86% yields, respectively. This procedure, however, was not general because in the other cases the hydrolysis was partial and significant amounts of intermediate amides and other by-products were generated, or the final acids did not precipitate on cooling. Fortunately, when the hydrolysis was performed in a refluxing mixture of conc. HCl and HOAc, *N*-nosyl β^3-amino acids **4a–e** were obtained in excellent yields after purification through a short silica gel column. Overall yields for the transformation of 1,2-amino alcohols into *N*-nosyl β^3-amino acids are summarized in Table 1.

Once we had a general, efficient and easily amenable to a large scale (5–50 mmol) methodology available for the homologation of natural α-amino acids to *N*-nosyl β^3-amino acids **4**, we turned our attention to their transformation into the corresponding Boc, Fmoc, and Cbz-derivatives that incorporate the usual protecting groups required for peptide synthesis. Taking into account that these groups can be removed under various conditions,[13b,c] we envisioned that protection of the carboxylic group as an allylic ester would constitute a general approach appropriate for our purposes.[17] On the other hand, although removal of the nosyl group may be carried out with either thiophenol or β-mercaptoethanol, our own experience suggested that the use of mercaptoacetic acid would be more convenient because the thioether formed as co-product can be easily removed by just washing the reaction mixture with a saturated aqueous solution of $NaHCO_3$.[8,14] In order to test



Scheme 3. (a) Allyl bromide, K_2CO_3, DMF, 17 h, then $HSCH_2CO_2H$, DBU, 5 h; (b) Boc_2O, Na_2CO_3, H_2O/dioxan, 0°C–rt, 16 h; (c) FmocCl, Na_2CO_3, H_2O/dioxan, 0°C–rt, 23 h; (d) BnOCOCl, Na_2CO_3, H_2O/dioxan, 0°C–rt, 17 h; (e) 1 M LiOH, MeOH, 17 h; (f) Bu_3SnH, $Pd(PPh_3)_4$, CH_2Cl_2, 10 min.



Scheme 4. (a) Allyl bromide, K_2CO_3, DMF, 18 h; (b) MeI, K_2CO_3, DMF, 17 h; (c) BuI, K_2CO_3, DMF, 19 h; (d) $HSCH_2CO_2H$, DBU, DMF, 17 h.

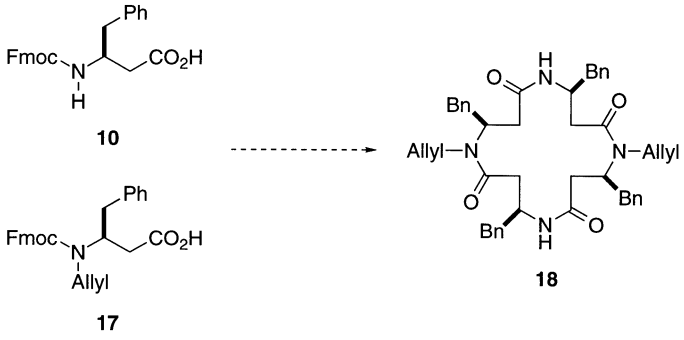
the aforementioned hypotheses, β^3-amino acid **4b** was chosen as a model and we focused our initial efforts on the preparation of the derivatives **9**–**11** shown in Scheme 3. As expected, one-pot reaction of **4b** with allyl bromide and K_2CO_3, followed by treatment with mercaptoacetic acid and DBU, in non-dried DMF furnished the key amino ester **5** in 66% yield. Reaction of **5** with Boc_2O, FmocCl, and BnOCOCl led almost quantitatively to the corresponding derivatives **6**–**8**. Finally, removal of the allyl group using LiOH/MeOH or $Bu_3SnH/Pd(PPh_3)_4$ provided **9**–**11** in 99, 58, and 84% yields, respectively.

Once established how to efficiently obtain *N*-protected β^3-amino acids we faced the preparation of their *N*-alkylated derivatives. These substrates are interesting because substitution on the nitrogen atom may play an important role in the conformational behavior of β-peptides.[18] Unfortunately, according to our experience, *N*-alkylation of Boc-β^3-amino esters is often troublesome and a careful selection of the conditions is necessary to reach good yields. In this context, the stability of the nosyl group to both acid and basic media, as well as the activation that it introduces into the NH moiety, suggested that a strategy based on the use of *N*-nosyl β^3-amino acids could be more appropriate.[19,20] In order to verify such hypotheses, amino acid **4b** was chosen as a model and converted to the key allylic ester **12** (see Scheme 4). As expected, reaction of **12** with either MeI or BuI smoothly furnished the alkylated derivatives **13** and **14** in almost quantitative yields. Finally, cleavage of nosyl group with mercaptoacetic acid and DBU afforded the corresponding *N*-alkyl β^3-amino esters **15** and **16** in good yields.

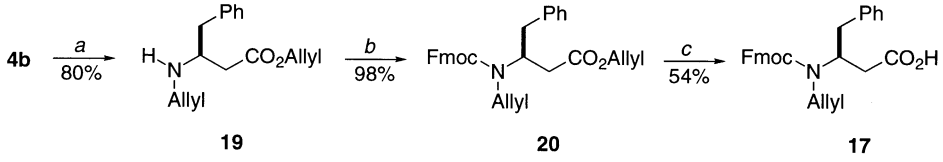
This approach has been fully exploited for the preparation of building block **17** which is useful for the solid phase synthesis of the previously reported scaffold **18** (see Scheme 5) to be used in combinatorial chemistry.[8]

In this case, the protection of the carboxyl function, the *N*-alkylation and the removal of the nosyl group were carried out in one-pot procedure, to furnish **19** in 80% yield (see Scheme 6). Finally, the protection of the amino group (98% yield) and the selective cleavage of the COO-Allyl group afforded the desired Fmoc β^3-amino acid **17** in 54% yield after recrystallization.

In summary, the methodology described in this paper provides a simple, efficient, and practical procedure for the homologation of natural α-amino acids to *N*-nosyl β^3-amino acids easily amenable to large-scale preparations.



Scheme 5.



Scheme 6. (a) Allyl bromide, K_2CO_3, DMF, 13 h, then $HSCH_2CO_2H$, DBU, 2.5 h; (b) FmocCl, Na_2CO_3, H_2O/dioxan, 0°C–rt, 24 h; (c) Bu_3SnH, $Pd(PPh_3)_4$, CH_2Cl_2, 2.5 h.

The stability of the nosyl group towards acids and bases, the activation that it introduces into the NH moiety, and the availability of smooth deprotection procedures confer to such *N*-nosyl amino acids a great synthetic utility. *N*-alkylation and transformation of *N*-nosyl β^3-amino acids into a variety of derivatives bearing the adequate functionality for peptide synthesis illustrate their potentiality.

3. Experimental

Melting points were taken on an electrothermal apparatus and have not been corrected. Specific rotations were determined at 20°C on a Perkin–Elmer 241 MC polarimeter. IR spectra were recorded on either a Perkin–Elmer 681 or a Nicolet 510 FT spectrometer and only the more representative frequencies (cm^{-1}) are reported. ^1H (300 MHz) and ^{13}C NMR (75.4 MHz) spectra were recorded on a Varian Unity Plus 300 spectrometer; ^1H NMR (500 MHz) spectra were recorded on a Varian Unity Inova 500 spectrometer; chemical shifts (δ) are quoted in ppm and referenced to internal TMS for ^1H NMR and $CDCl_3$ (δ 77.0) or CD_3OD (δ 49.0) for ^{13}C NMR; data are reported as follows: s, singlet; d, doublet; t, triplet; q, quartet; hep, heptuplet; m, multiplet; br, broad; where appropriate, 2D techniques were also used to assist in structure elucidation. High-resolution mass spectra (HRMS) were obtained from the Centro de Apoio Cientifico Tecnoloxico a Investigacion (C.A.C. T.I.), Universidad de Vigo. Elemental analyses were obtained by the Servei de Microanàlisi (CID-CSIC, Barcelona). Flash chromatography was performed on SDS silica gel (35–70 μm). Analytical thin-layer chromatography was carried out on Merck Kieselgel 60 F_{254} plates. The following solvents and reagents were purified and dried according to standard procedures: CH_2Cl_2, DMF, and pyridine. All other reagents were used as received. The following compounds have been reported previously: (*S*)-*N*-*p*-nitrobenzenesulfonyl-2-benzylaziridine (**2b**) and (*S*)-3-[*p*-nitrobenzenesulfonyl]amino-4-phenylbutanoic acid (**4b**).[8]

3.1. Preparation of *N*-*p*-nitrobenezenesulfonyl β^3-amino acids. General procedure

p-Nitrobenzenesulfonyl chloride (13.3 g, 60 mmol) was added in one portion to a suspension of amino alcohols **1** (20 mmol) in dry 2:1 CH_2Cl_2/pyridine (20 mL) at 0°C and the resulting mixture was stirred at room temperature for 2–4 h. It was diluted with CH_2Cl_2 (300 mL) and washed with 2 M HCl (3×100 mL), which was subsequently extracted with CH_2Cl_2 (50 mL). The organic portions were combined and carefully shaken (CAUTION: undesirable emulsions are produced under vigorous shaking) with a 2 M aqueous solution of KOH (6×200 mL) and the aqueous portions were subsequently extracted with CH_2Cl_2 (150 mL). The organic portions were combined, dried (Na_2SO_4) and the solvent was removed to afford *N*-(*p*-nitrobenzenesulfonyl)aziridines **2** (**2a**: 98%; **2b**: 95%; **2c**: 91%; **2d**: 91%; **2e**: 90%; **2f**: 97%) that were used in the next step without further purification. Analytical samples were purified by flash chromatography (CH_2Cl_2) or recrystallization (CH_2Cl_2/hexanes) to afford pure aziridines **2** as white solids.

NaCN (1.47 g, 30 mmol, 1.5 equiv.) was added in one portion to a suspension of crude aziridines **2** in 4:1 CH_3CN/H_2O (100 mL) and the resulting mixture stirred vigorously at room temperature for 24 h. The final solution was partitioned in CH_2Cl_2 (250 mL) and a saturated aqueous solution of NH_4Cl (250 mL). The aqueous layer was further extracted with CH_2Cl_2 (3×50 mL), the organic portions were combined, dried (Na_2SO_4) and the solvent removed to afford the crude nitriles **3** as dark brown solids or viscous oils (**3a**: 86% from **1**; **3b**: 88%; **3c**: 77%; **3d**: 70%; **3e**: 70%) that were used without further purification in the next step. Analytical samples were purified by flash chromatography (CH_2Cl_2/CH_3OH 98:2) to afford pure nitriles **3** as solids.

Crude nitriles **3** in 4:1 conc. HCl/HOAc (200 mL) were heated at reflux for 4 h. After cooling, the solution was extracted with CH_2Cl_2 (5×200 mL), dried (Na_2SO_4) and the solvent removed. The residue was purified by flash chromatography (CH_2Cl_2/CH_3OH 95:5) to furnish pure *N*-*p*-nitrobenezenesulfonyl β^3-amino acids **4**.

3.1.1. (*S*)-*N*-*p*-Nitrobenzenesulfonyl-2-methylaziridine (2a). White solid; R_f=0.50 (CH_2Cl_2); mp 86–88°C; $[\alpha]_D$=+24.5 (c=1.0 in $CHCl_3$); IR (KBr): ν 3105, 2975, 2935, 1609, 1532, 1355, 1331, 1304, 1156; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.40 (2H, d, J=9.0 Hz, ArH), 8.16 (2H, d, J=9.0 Hz, ArH), 3.05–2.90 (1H, m, NCH), 2.74 (1H, d, J=7.0 Hz, NCH_aH_b), 2.13 (1H, d, J=4.9 Hz, NCH$_a$$H_b$), 1.31 (3H, d, J=5.6 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 150.6, 144.3, 129.1, 124.3, 36.8, 35.5, 16.8; HRMS (FAB): calcd for $[M+H]^+$ $C_9H_{11}N_2O_4S$: 243.0440; found: 243.0442.

3.1.2. (*S*)-*N*-*p*-Nitrobenzenesulfonyl-2-isobutylaziridine (2c). White solid; R_f=0.50 (CH_2Cl_2); mp 35–37°C; $[\alpha]_D$=+9.3 (c=1.0 in $CHCl_3$); IR (KBr): ν 3100, 2980, 2880, 1610, 1530, 1360, 1340, 1310, 1165; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.39 (2H, d, J=9.1 Hz, ArH), 8.16 (2H, d, J=9.1 Hz, ArH), 3.00–2.90 (1H, m, NCH), 2.74 (1H, d, J=7.2 Hz, NCH_aH_b), 2.12 (1H, d, J=4.7 Hz, NCH$_a$$H_b$), 1.75–1.55 (1H, m, C$H$($CH_3$)$_2$), 1.40–1.35 (2H, m, C$H_2$CH($CH_3$)$_2$), 0.92 (3H, d, J=6.6 Hz, CH_3), 0.91 (3H, d, J=6.7 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 150.6, 144.2, 129.2, 124.2, 40.3, 40.0, 34.8, 26.8, 22.7, 21.9; HRMS (FAB): calcd for $[M+H]^+$ $C_{12}H_{17}N_2O_4S$: 285.0909; found: 285.0900.

3.1.3. (*S*)-*N*-*p*-Nitrobenzenesulfonyl-2-isopropylaziridine (2d). White solid; R_f=0.50 (CH_2Cl_2); mp 73–76°C; $[\alpha]_D$=+11.2 (c=1.0 in $CHCl_3$); IR (KBr): ν 3120, 2980, 2890, 1620, 1540, 1360, 1340, 1325, 1175, 950; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.39 (2H, d, J=9.2 Hz, ArH), 8.16 (2H, d, J=9.2 Hz, ArH), 2.75–2.65 (2H, m, NCH and NCH_aH_b), 2.22–2.18 (1H, m, NCH$_a$$H_b$), 1.55–1.40 (1H, m, C$H$($CH_3$)$_2$), 0.94 (3H, d, J=6.9 Hz, CH_3), 0.84 (3H, d, J=6.7 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 150.6, 144.1, 129.3, 124.2, 47.0, 33.6, 30.1, 19.5, 19.0; HRMS (FAB): calcd for $[M+H]^+$ $C_{11}H_{15}N_2O_4S$: 271.0753; found: 271.0762.

3.1.4. (*S*)-*N*-*p*-Nitrobenzenesulfonyl-2-*tert*-butylaziridine (2e). White solid; R_f=0.55 (CH_2Cl_2); mp 114–115°C; $[\alpha]_D$=+29.8 (c=1.0 in $CHCl_3$); IR (KBr): ν 3100, 2980,

2860, 1605, 1525, 1370, 1345, 1300, 1175; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.39 (2H, d, J=9.2 Hz, ArH), 8.17 (2H, d, J=9.2 Hz, ArH), 2.74 (1H, dd, J=7.2, 4.9 Hz, NCH), 2.63 (1H, dd, J=7.2, 0.5 Hz, NCH_aH_b), 2.23 (1H, dd, J=4.9, 0.5 Hz, NCH$_a$$H_b$), 0.83 (9H, s, C(CH$_3$)$_3$); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 144.2, 135.5, 129.4, 124.2, 49.7, 31.3, 30.3, 26.2; HRMS (FAB): calcd for $[M+H]^+$ $C_{12}H_{17}N_2O_4S$: 285.0909; found: 285.0903.

3.1.5. (*S*)-*N*-*p*-Nitrobenzenesulfonyl-2-phenylaziridine (2f). White solid; R_f=0.50 (CH_2Cl_2); mp 120–122°C; $[\alpha]_D$=+77.8 (c=1.0 in $CHCl_3$); IR (KBr): ν 3100, 3030, 1610, 1530, 1520, 1350, 1330, 1310, 1160; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.38 (2H, d, J=9.1 Hz, ArH), 8.19 (2H, d, J=9.1 Hz, ArH), 7.40–7.20 (5H, m, ArH), 3.90 (1H, dd, J=7.1, 4.6 Hz, NCH), 3.11 (1H, d, J=7.1 Hz, NCH_aH_b), 2.51 (1H, d, J=4.6 Hz, NCH$_a$$H_b$); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 150.6, 144.0, 134.1, 129.2, 128.8, 126.4, 124.4, 41.9, 36.6; HRMS (FAB): calcd for $[M+H]^+$ $C_{14}H_{13}N_2O_4S$: 305.0596; found: 305.0594.

3.1.6. (*S*)-3-[*p*-Nitrobenzenesulfonyl]aminobutanenitrile (3a). Yellowish solid; R_f=0.40 (CH_2Cl_2/CH_3OH 98:2); mp 155–157°C; $[\alpha]_D$=−51.5 (c=1.0 in $CHCl_3$); IR (KBr): ν 3267, 3110, 2977, 2252, 1609, 1534, 1355, 1312, 1167, 1146; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.40 (2H, d, J=9.1 Hz, ArH), 8.09 (2H, d, J=9.1 Hz, ArH), 5.00–4.90 (1H, br s, NH), 3.85–3.70 (1H, m, NCH), 2.68 (1H, dd, J=16.8, 5.7 Hz, CH_aH_bCN), 2.57 (1H, dd, J=16.8, 4.4 Hz, CH$_a$$H_b$CN), 1.30 (3H, d, J=6.7 Hz, CH$_3$); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 150.3, 146.1, 128.2, 124.6, 116.1, 46.7, 26.5, 20.7; HRMS (FAB): calcd for $[M+H]^+$ $C_{10}H_{12}N_3O_4S$: 270.0549; found: 270.0558.

3.1.7. (*S*)-3-[*p*-Nitrobenzenesulfonyl]amino-4-phenylbutanenitrile (3b). Yellowish solid; R_f=0.50 (CH_2Cl_2/CH_3OH 98:2); mp 116–118°C; $[\alpha]_D$=−66.7 (c=1.0 in $CHCl_3$); IR (KBr): ν 3260, 3110, 2980, 2920, 2240, 1605, 1520, 1345, 1315, 1305, 1160; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.15 (2H, d, J=9.0 Hz, ArH), 7.71 (2H, d, J=9.0 Hz, ArH), 7.20–7.10 (3H, m, ArH), 7.00–6.90 (2H, m, ArH), 5.34 (1H, br d, J=7.2 Hz, NH), 3.75–3.65 (1H, m, NCH), 2.96 (1H, dd, J=14.0, 5.6 Hz, CH_aH_b), 2.86 (1H, dd, J=16.9, 5.9 Hz, CH_xH_y), 2.79 (1H, dd, J=14.0, 9.1 Hz, CH$_a$$H_b$), 2.69 (1H, dd, J=16.9, 4.1 Hz, CH$_x$$H_y$); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 149.9, 145.0, 135.0, 129.0, 128.9, 127.9, 127.5, 124.3, 116.5, 52.3, 39.9, 25.4; HRMS (FAB): calcd for $[M+H]^+$ $C_{16}H_{16}N_3O_4S$: 346.0862; found: 346.0873.

3.1.8. (*S*)-5-Methyl-3-[*p*-nitrobenzenesulfonyl]aminohexanenitrile (3c). Yellowish solid; R_f=0.45 (CH_2Cl_2/CH_3OH 98:2); mp 79–82°C; $[\alpha]_D$=−59.8 (c=1.0 in $CHCl_3$); IR (KBr): ν 3204, 2960, 2265, 1609, 1542, 1434, 1349, 1167, 1092; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.39 (2H, d, J=9.1 Hz, ArH), 8.10 (2H, d, J=9.1 Hz, ArH), 5.45–4.25 (1H, br s, NH), 3.70–3.55 (1H, m, NCH), 2.75 (1H, dd, J=16.9, 5.5 Hz, CH_aH_bCN), 2.54 (1H, dd, J=16.9, 3.8 Hz, CH$_a$$H_b$CN), 1.60–1.35 (3H, m, C$H_2CH$(CH$_3$)$_2$), 0.84 (3H, d, J=6.3 Hz, CH$_3$), 0.66 (3H, d, J=6.3 Hz, CH$_3$); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 150.2, 146.1, 128.3, 124.5, 116.5, 48.8, 43.1, 25.6, 24.4, 22.5, 21.4; HRMS (FAB): calcd for $[M+H]^+$ $C_{13}H_{18}N_3O_4S$: 312.1018; found: 312.1009.

3.1.9. (*R*)-4-Methyl-3-[*p*-nitrobenzenesulfonyl]aminopentanenitrile (3d). Yellowish solid; R_f=0.50 (CH_2Cl_2/CH_3OH 98:2); mp 116–117°C; $[\alpha]_D$=−77.6 (c=1.0 in $CHCl_3$); IR (KBr): ν 3320, 3120, 2980, 2250, 1610, 1535, 1345, 1340, 1170, 1150; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.39 (2H, d, J=9.1 Hz, ArH), 8.09 (2H, d, J=9.1 Hz, ArH), 5.13 (1H, br d, J=8.4 Hz, NH), 3.40–3.25 (1H, m, NCH), 2.69 (1H, dd, J=16.9, 5.5 Hz, CH_aH_bCN), 2.62 (1H, dd, J=16.9, 5.0 Hz, CH$_a$$H_b$CN), 2.00–1.85 (1H, m, C$H$(CH$_3$)$_2$), 0.88 (3H, d, J=6.7 Hz, CH$_3$), 0.83 (3H, d, J=6.7 Hz, CH$_3$); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 150.2, 146.0, 128.3, 124.5, 116.6, 56.3, 31.4, 23.0, 19.1, 18.0; HRMS (FAB): calcd for $[M+H]^+$ $C_{12}H_{16}N_3O_4S$: 298.0862; found: 298.0863.

3.1.10. (*R*)-4,4-Dimethyl-3-[*p*-nitrobenzenesulfonyl]-aminopentanenitrile (3e). Yellowish solid; R_f=0.55 (CH_2Cl_2/CH_3OH 98:2); mp 137–138°C; $[\alpha]_D$=−40.3 (c=0.8 in $CHCl_3$); IR (KBr): ν 3298, 3110, 2971, 2252, 1610, 1578, 1532, 1351, 1165; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.38 (2H, d, J=9.1 Hz, ArH), 8.12 (2H, d, J=9.1 Hz, ArH), 5.30–5.25 (1H, br s, NH), 3.44 (1H, t, J=5.5 Hz, NCH), 2.64 (1H, dd, J=17.2, 5.5 Hz, CH_aH_bCN), 2.52 (1H, dd, J=17.2, 5.5 Hz, CH$_a$$H_b$CN), 0.92 (9H, s, C(CH$_3$)$_3$); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 150.2, 146.3, 128.4, 124.5, 117,4, 59.2, 35.3, 26.4, 20.7; HRMS (FAB): calcd for $[M+H]^+$ $C_{13}H_{18}N_3O_4S$: 312.1018; found: 312.1011.

3.1.11. (*S*)-3-[*N*-*p*-Nitrobenzenesulfonyl]aminobutanoic acid (4a). White solid; R_f=0.30 (CH_2Cl_2/CH_3OH 95:5); mp 122–124°C; $[\alpha]_D$=−7.1 (c=1.0 in EtOH); IR (KBr): ν 3400–2900 (br), 3272, 3116, 2950, 1717, 1610, 1528, 1348, 1310, 1170; ^{1}H NMR (CD_3OD, 300 MHz) δ 8.38 (2H, d, J=9.0 Hz, ArH), 8.08 (2H, d, J=9.0 Hz, ArH), 3.80–3.65 (1H, m, NCH), 2.44 (1H, dd, J=15.7, 6.6 Hz, CH_aH_bCO$_2$), 2.33 (1H, dd, J=15.7, 7.0 Hz, CH$_a$$H_bCO_2$), 1.11 (3H, d, J=6.9 Hz, CH$_3$); ^{13}C NMR (CD_3OD, 75.4 MHz) δ 175.0, 152.2, 149.7, 130.2, 126.2, 49.2, 43.6, 22.7; HRMS (FAB): calcd for $[M+H]^+$ $C_{10}H_{13}N_2O_6S$: 289.0494; found: 289.0489.

3.1.12. (*S*)-5-Methyl-3-[*p*-nitrobenzenesulfonyl]aminohexanoic acid (4c). Yellowish oil; R_f=0.30 (CH_2Cl_2/CH_3OH 95:5); $[\alpha]_D$=+2.9 (c=0.7 in EtOH); IR (film): ν 3400–2800 (br), 3290, 3110, 2960, 1715, 1610, 1535, 1355, 1165; ^{1}H NMR (CD_3OD, 300 MHz) δ 8.38 (2H, d, J=9.1 Hz, ArH), 8.08 (2H, d, J=9.1 Hz, ArH), 3.75–3.65 (1H, m, NCH), 2.32 (2H, d, J=6.6 Hz, CH$_2$CO$_2$), 1.65–1.45 (1H, m, CH(CH$_3$)$_2$), 1.45–1.32 (1H, m, CH_aH_bCH(CH$_3$)$_2$), 1.30–1.20 (1H, m, CH$_a$$H_b$CH(CH$_3$)$_2$), 0.83 (3H, d, J=6.6 Hz, CH$_3$), 0.72 (3H, d, J=6.6 Hz, CH$_3$); ^{13}C NMR (CD_3OD, 75.4 MHz) δ 174.6, 151.3, 149.1, 129.4, 125.3, 50.8, 45.7, 41.9, 25.6, 23.3, 21.9; HRMS (FAB): calcd for $[M+H]^+$ $C_{13}H_{19}N_2O_6S$: 331.0964; found: 331.0978.

3.1.13. (*R*)-4-Methyl-3-[*p*-nitrobenzenesulfonyl]aminopentanoic acid (4d). White solid; R_f=0.30 (CH_2Cl_2/CH_3OH 95:5); mp 153–155°C; $[\alpha]_D$=+44.8 (c=1.0 in EtOH); IR (KBr): ν 3400–2900 (br), 3200, 2970, 1725, 1610, 1535, 1350, 1155, 1140; ^{1}H NMR (CD_3OD, 300 MHz) δ 8.36 (2H, d, J=9.1 Hz, ArH), 8.06 (2H, d, J=9.1 Hz, ArH), 3.65–3.55 (1H, m, NCH), 2.34 (1H, dd,

J=15.7, 5.6 Hz, C$H_aH_bCO_2$), 2.19 (1H, dd, J=15.7, 7.5 Hz, $CH_aH_bCO_2$), 1.82 (1H, hepd, J=6.9, 4.9 Hz, C$H(CH_3)_2$), 0.87 (3H, d, J=6.9 Hz, CH_3), 0.86 (3H, d, J=6.9 Hz, CH_3); ^{13}C NMR (CD_3OD, 75.4 MHz) δ 174.6, 151.2, 149.2, 129.3, 125.2, 57.8, 37.9, 33.7, 18.9, 18.1; HRMS (FAB): calcd for $[M+H]^+$ $C_{12}H_{17}N_2O_6S$: 317.0807; found: 317.0805. Anal. Calcd for $C_{12}H_{16}N_2O_6S$: C, 45.64; H, 5.10; N, 8.86. Found: C, 45.64; H, 5.14; N, 8.89.

3.1.14. (*R*)-4,4-Dimethyl-3-[*p*-nitrobenzenesulfonyl]-aminopentanoic acid (4e). White solid; R_f=0.25 (CH_2Cl_2/CH_3OH 95:5); mp 184–186°C; $[\alpha]_D$=+73.0 (c=1.0 in EtOH); IR (KBr): ν 3500–2900 (br), 3232, 3110, 2970, 1723, 1607, 1528, 1349, 1335, 1310, 1146, 1074; ^{1}H NMR (CD_3OD, 300 MHz) δ 8.33 (2H, d, J=9.1 Hz, ArH), 8.04 (2H, d, J=9.1 Hz, ArH), 3.64 (1H, dd, J=7.8, 4.4 Hz, NCH), 2.49 (1H, dd, J=16.1, 4.4 Hz, C$H_aH_bCO_2$), 2.05 (1H, dd, J=16.1, 7.8 Hz, $CH_aH_bCO_2$), 0.92 (9H, s, C$(CH_3)_3$); ^{13}C NMR (CD_3OD, 75.4 MHz) δ 175.1, 151.2, 149.5, 129.3, 125.1, 61.3, 37.4, 36.1, 26.8; HRMS (FAB): calcd for $[M+H]^+$ $C_{13}H_{19}N_2O_6S$: 331.0964; found: 331.0971. Anal. Calcd for $C_{13}H_{18}N_2O_6S$: C, 47.27; H, 5.49; N, 8.48. Found: C, 46.91; H, 5.46; N, 8.25.

3.2. Preparation of *N*-protected β^3-amino acids

3.2.1. Allyl (*S*)-3-amino-4-phenylbutanoate (5). Anhydrous K_2CO_3 (0.77 g, 5.6 mmol) was added in one portion to a stirred solution of **4b** (2.03 g, 5.6 mmol) and allyl bromide (0.48 mL, 5.5 mmol) in non-dried DMF (20 mL) at room temperature. After 17 h mercaptoacetic acid (0.93 mL, 13.4 mmol) was added followed by DBU (8.30 mL, 55.6 mmol) and the mixture stirred for a further 5 h. The resulting suspension was diluted with EtOAc (50 mL), washed with a saturated aqueous solution of $NaHCO_3$ (3×50 mL), dried ($MgSO_4$) and the solvent removed to afford **5** (0.81 g, 66%) as an orange oil: R_f=0.42 (CH_2Cl_2/MeOH 10:1); $[\alpha]_D$=+0.2 (c=1.1 in $CHCl_3$); IR (film): ν 3340, 2900, 1720, 1450, 1140; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.29–7.24 (2H, m, ArH), 7.21–7.16 (3H, m, ArH), 5.88 (1H, ddt, J=17.0, 10.5, 5.5 Hz, CH_2CH=CH_2), 5.29 (1H, ddd, J=17.0, 3.0, 1.5 Hz, CH_2CH=CH_aH_b), 5.20 (1H, ddd, J=10.5, 2.5, 1.5 Hz, CH_2CH=CH_aH_b), 4.57–4.54 (2H, m, CH_2CH=CH_2), 3.49–3.43 (1H, m, NCH), 2.74 (1H, dd, J=13.5, 5.5 Hz, CH_aH_bAr), 2.59 (1H, dd, J=13.5, 8.0 Hz, CH_aH_bAr), 2.50 (1H, dd, J=16.0, 4.0 Hz, CH_aH_bCO), 2.33 (1H, dd, J=16.0, 9.0 Hz, CH_aH_bCO); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 171.9, 138.4, 132.0, 129.2, 128.5, 126.5, 118.3, 65.1, 49.6, 43.9, 41.8; HRMS (FAB): calcd for $[M+H]^+$ $C_{13}H_{18}NO_2$: 220.1337; found: 220.1335.

3.2.2. Allyl (*S*)-3-*tert*-butoxycarbonylamino-4-phenylbutanoate (6). Boc_2O (0.96 g, 4.4 mmol) was added in small portions to a suspension of **5** (0.74 g, 3.4 mmol) and Na_2CO_3 (0.90 g, 8.5 mmol) in 2:1 H_2O/dioxan (15 mL) at 0°C and the resulting mixture was stirred at room temperature for 16 h. The mixture was diluted with EtOAc (50 mL) and washed with a 0.5 M aqueous solution of citric acid (3×50 mL), which was subsequently extracted with EtOAc (25 mL). The organic portions were combined, washed with brine (50 mL), dried ($MgSO_4$) and the solvent removed to afford **6** (1.01 g, 94%) as a yellow oil: R_f=0.68 (hexanes/EtOAc 3:1); $[\alpha]_D$=−8.7 (c=1.1 in $CHCl_3$); IR (film): ν 3370, 2980, 1710, 1500, 1165; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.34–7.17 (5H, m, ArH), 5.92 (1H, ddt, J=16.7, 11.3, 5.4 Hz, CH_2CH=CH_2), 5.40–5.20 (2H, m, CH_2CH=CH_2), 5.06 (1H, br d, J=7.2 Hz, NH), 4.62–4.56 (2H, m, CH_2CH=CH_2), 4.26–4.08 (1H, m, NCH), 2.92 (1H, dd, J=13.2, 6.7 Hz, CH_aH_bAr), 2.81 (1H, dd, J=13.2, 7.8 Hz, CH_aH_bAr), 2.56 (1H, dd, J=15.8, 5.4 Hz, CH_aH_bCO), 2.45 (1H, dd, J=15.8, 6.0 Hz, CH_aH_bCO), 1.40 (9H, s, C$(CH_3)_3$); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 171.2, 155.0, 137.6, 131.8, 129.3, 128.4, 126.4, 118.4, 79.3, 65.2, 48.8, 40.3, 37.6, 28.3; HRMS (FAB): calcd for $[M+H]^+$ $C_{18}H_{26}NO_4$: 320.1862; found: 320.1867.

3.2.3. (*S*)-3-*tert*-Butoxycarbonylamino-4-phenylbutanoic acid (9). A 1 M aqueous solution of LiOH (30 mL, 30 mmol) was added to a stirred solution of **6** (1.05 g, 3.3 mmol) in CH_3OH (50 mL). After 17 h the solution was concentrated under reduced pressure and the resulting suspension diluted with EtOAc (100 mL) and washed with a 0.5 M aqueous solution of citric acid (3×50 mL), which was subsequently extracted with EtOAc (25 mL). The organic portions were combined, washed with brine (50 mL), dried ($MgSO_4$) and the solvent removed to afford **9** (0.91 g, 99%) as a white solid, similar in all respects to a commercially available sample (Fluka Chimie AG).

3.2.4. Allyl (*S*)-3-(9*H*-fluoren-9-yl)methoxycarbonylamino-4-phenylbutanoate (7). (9*H*-Fluoren-9-yl)methyl chloroformate (2.86 g, 11.1 mmol) was added in small portions to a suspension of **5** (2.02 g, 9.2 mmol) and Na_2CO_3 (2.44 g, 23.1 mmol) in 2:1 H_2O/dioxan (30 mL) at 0°C and the resulting mixture was stirred at room temperature for 23 h. The mixture was diluted with EtOAc (200 mL), washed with a 0.5 M aqueous solution of citric acid (3×50 mL) and brine (50 mL), dried ($MgSO_4$) and the solvent removed to afford **7** (3.91 g, 96%) as a creamy solid: R_f=0.45 (hexanes/EtOAc 3:1); mp 114–115°C; $[\alpha]_D$=−12.7 (c=1.1 in $CHCl_3$); IR (KBr): ν 3300, 3040, 2920, 1710, 1440, 1230; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.80–7.72 (2H, m, ArH), 7.74–7.50 (2H, m, ArH), 7.44–7.10 (9H, m, ArH), 5.90 (1H, ddt, J=17.1, 10.5, 5.7 Hz, CH_2CH=CH_2), 5.36–5.20 (3H, m, CH_2CH=CH_2 and NH), 4.60–4.57 (2H, m, CH_2CH=CH_2), 4.46–4.00 (4H, m, CHN and CHCH_2O), 3.00–2.75 (2H, m, CH_2Ar), 2.60–2.40 (2H, m, CH_2CO); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 171.1, 155.6, 143.9, 141.3, 137.4, 131.8, 129.3, 128.6, 127.3, 127.0, 126.7, 125.0, 120.0, 118.6, 66.6, 65.3, 49.3, 47.2, 40.2, 37.5; HRMS (FAB): calcd for $[M+H]^+$ $C_{28}H_{28}NO_4$: 442.2018; found: 442.1997.

3.2.5. (*S*)-3-(9*H*-Fluoren-9-yl)methoxycarbonylamino-4-phenylbutanoic acid (10). To a stirred solution of **7** (3.87 g, 8.8 mmol) in dry CH_2Cl_2 (60 mL) was added $Pd(PPh_3)_4$ (100 mg, 87 μmol) quickly followed by Bu_3SnH (3.50 mL, 13.0 mmol) and the resulting mixture stirred under N_2 for 10 min. The solution was washed with 2 M HCl (2×30 mL) and brine (30 mL), dried ($MgSO_4$) and the solvent removed. The residue was dissolved in CH_3CN (150 mL), washed with hexanes (3×150 mL), the solvent removed and the resulting solid recrystallized from CCl_4 to afford **10** (2.03 g, 58%) as a white solid, similar in all respects to a commercially available sample (Fluka Chimie AG).

3.2.6. Allyl (*S*)-3-benzyloxycarbonylamino-4-phenylbutanoate (8). Benzyl chloroformate (0.70 mL, 5.0 mmol) was added dropwise to a suspension of **5** (0.91 g, 4.1 mmol) and Na_2CO_3 (1.11 g, 10.4 mmol) in 2:1 H_2O/dioxan (15 mL) at 0°C and the resulting mixture was stirred at room temperature for 17 h. The mixture was diluted with EtOAc (50 mL), washed with a 0.5 M aqueous solution of citric acid (3×50 mL) and brine (50 mL), dried ($MgSO_4$) and the solvent removed to afford **8** (1.44 g, 98%) as a yellow oil: R_f=0.55 (hexanes/EtOAc 3:1); $[\alpha]_D$=−12.8 (c=1.0 in $CHCl_3$); IR (film): ν 3320, 3000, 1710, 1505, 1240; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.36–7.12 (10H, m, ArH), 5.88 (1H, ddt, J=17.2, 10.2, 5.8 Hz, CH_2CH=CH_2), 5.40–5.18 (3H, m, NH and CH_2CH=CH_2), 5.06 (2H, s, OCH_2Ar), 4.60–4.50 (2H, m, CH_2CH=CH_2), 4.32–4.14 (1H, m, NCH), 2.90 (1H, dd, J=13.4, 6.6 Hz, CH_aH_bAr), 2.82 (1H, dd, J=13.4, 7.4 Hz, CH_aH_bAr), 2.56 (1H, dd, J=16.2, 5.4 Hz, CH_aH_bCO), 2.47 (1H, dd, J=16.2, 5.4 Hz, CH_aH_bCO); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 170.9, 155.4, 137.3, 136.3, 131.7, 129.1, 128.3, 128.2, 127.8, 127.7, 124.4, 118.4, 66.4, 65.1, 49.3, 40.1, 37.5; HRMS (FAB): calcd for $[M+H]^+$ $C_{21}H_{23}NO_4$: 354.1705; found: 354.1717.

3.2.7. (*S*)-3-Benzyloxycarbonylamino-4-phenylbutanoic acid (11). A 1 M aqueous solution of LiOH (20 mL, 20 mmol) was added to a stirred solution of **8** (778 mg, 2.20 mmol) in CH_3OH (20 mL). After 17 h the solution was concentrated under reduced pressure and the resulting suspension diluted with EtOAc (50 mL) and washed with a 0.5 M aqueous solution of citric acid (3×50 mL), which was subsequently extracted with EtOAc (25 mL). The organic portions were combined, washed with brine (50 mL), dried ($MgSO_4$) and the solvent removed. The residue was purified by recrystallization from CCl_4/hexanes to afford **11** (580 mg, 84%) as a white solid, similar in all respects to a commercially available sample (Fluka Chimie AG).

3.3. Preparation of *N*-alkylated derivatives

3.3.1. Allyl (*S*)-3-[*p*-nitrobenzenesulfonyl]amino-4-phenylbutanoate (12). Anhydrous K_2CO_3 (456 mg, 3.3 mmol) was added in one portion to a solution of **4b** (1.092 g, 3.0 mmol) and allyl bromide (0.31 mL, 3.6 mmol) in dry DMF (20 mL) at room temperature. The resulting mixture was stirred at room temperature under N_2 for 18 h. Removal of the volatiles afforded a brown solid that was diluted with EtOAc (50 mL), washed with a 0.75 M aqueous solution of citric acid (2×50 mL) and brine (50 mL), and dried ($MgSO_4$). The solvent was removed to afford **12** (1.123 g, 93%) as a brown solid that was used in the next step without further purification. An analytical sample was purified by flash chromatography (hexanes/EtOAc 1:1) to afford pure **12** as a yellowish solid: R_f=0.52 (hexanes/EtOAc 1:1); mp 87–90°C; $[\alpha]_D$=−49.4 (c=1.0 in $CHCl_3$); IR (KBr): ν 3320, 3270, 3100, 2970, 1735, 1725, 1610, 1525, 1350, 1310, 1160; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.13 (2H, d, J=9.0 Hz, ArH), 7.76 (2H, d, J=9.0 Hz, ArH), 7.17–7.08 (3H, m, ArH), 7.00–6.95 (2H, m, ArH), 5.89 (1H, ddt, J=17.2, 10.4, 5.8 Hz, CH_2CH=CH_2), 5.60 (1H, d, J=8.7 Hz, NH), 5.35–5.23 (2H, m, CH_2CH=CH_2), 4.65–4.50 (2H, m, CH_2CH=CH_2), 3.90–3.75 (1H, m, NCH), 2.85 (1H, dd, J=13.8, 6.0 Hz, CH_aH_b), 2.75 (1H, dd, J=13.8, 8.3 Hz, CH_aH_b), 2.66 (2H, d, J=5.5 Hz, CH_2); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 170.8, 149.6, 145.9, 136.6, 131.5, 129.1, 128.6, 127.9, 126.9, 124.0, 118.9, 65.5, 52.8, 40.7, 39.1; HRMS (FAB): calcd for $[M+H]^+$ $C_{19}H_{21}N_2O_6S$: 405.1120; found: 405.1102.

3.3.2. Allyl (*S*)-3-[*N*-methyl-*N*-*p*-nitrobenzenesulfonyl]-amino-4-phenylbutanoate (13). Anhydrous K_2CO_3 (552 mg, 4.0 mmol) was added in one portion to a solution of crude **12** (404 mg, 1.0 mmol) and MeI (0.25 mL, 4.0 mmol) in dry DMF (5 mL) at room temperature. The resulting mixture was stirred at room temperature under N_2 for 17 h. Removal of the volatiles afforded a brown solid that was diluted with EtOAc (40 mL), washed with a 0.75 M aqueous solution of citric acid (2×40 mL), and brine (40 mL) and dried ($MgSO_4$). The solvent was removed to afford **13** (402 mg, 95%) as a dark oil that was used in the next step without further purification. An analytical sample was purified by flash chromatography (CH_2Cl_2) to afford pure **13** as a white solid; R_f=0.50 (CH_2Cl_2); mp 112–114°C; $[\alpha]_D$=−12.5 (c=0.8 in $CHCl_3$); IR (KBr): ν 3040, 2980, 1740, 1610, 1525, 1340, 1170; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.12 (2H, d, J=9.0 Hz, ArH), 7.62 (2H, d, J=9.0 Hz, ArH), 7.25–7.15 (3H, m, ArH), 7.10–7.00 (2H, m, ArH), 5.88 (1H, ddt, J=17.2, 10.4, 5.9 Hz, CH_2CH=CH_2), 5.30 (1H, dq, J=17.2, 1.5 Hz, CH_2CH=CH_aH_b), 5.25–5.20 (1H, m, CH_2CH=CH_aH_b), 4.75–4.65 (1H, m, NCH), 4.51 (2H, ddd, J=5.9, 2.8, 1.5 Hz, CH_2CH=CH_2), 2.85 (3H, s, NCH_3), 2.84 (1H, dd, J=13.9, 6.4 Hz, CH_xH_y), 2.73 (1H, dd, J=13.9, 8.8 Hz, CH_xH_y), 2.65–2.55 (2H, m, CH_2); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 170.0, 149.6, 145.4, 137.1, 131.7, 129.0, 128.7, 128.2, 127.0, 124.0, 118.8, 65.7, 56.8, 38.9, 37.9, 28.8; HRMS (FAB): calcd for $[M+H]^+$ $C_{20}H_{23}N_2O_6S$: 419.1277; found: 419.1292.

3.3.3. Allyl (*S*)-3-methylamino-4-phenylbutanoate (15). Mercaptoacetic acid (114 μL, 1.6 mmol) and DBU (750 μL, 5.0 mmol) were added to a solution of crude **13** (210 mg, 0.5 mmol) in non-dried DMF (5 mL) under N_2 at room temperature. The resulting mixture was stirred for 19 h, concentrated under reduced pressure and diluted with EtOAc (30 mL), which was washed with a saturated solution of $NaHCO_3$ (2×30 mL), and brine (30 mL) and dried ($MgSO_4$). The solvent was removed to afford a brown solid that was purified by flash chromatography (hexanes/EtOAc 1:1) to give **15** (71 mg, 60%) as a yellow oil; R_f=0.45 (hexanes/EtOAc 1:1); $[\alpha]_D$=+8.1 (c=1.3 in $CHCl_3$); IR (film): ν 3040, 2980, 2970, 1740, 1150; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.35–7.15 (5H, m, ArH), 5.91 (1H, ddt, J=17.2, 10.4, 5.8 Hz, CH_2CH=CH_2), 5.32 (1H, dq, J=17.2, 1.5 Hz, CH_2CH=CH_aH_b), 5.25–5.20 (1H, m, CH_2CH=CH_aH_b), 4.60–4.55 (2H, m, CH_2CH=CH_2), 3.25–3.10 (1H, m, NCH), 2.84 (1H, dd, J=13.4, 6.6 Hz, CH_aH_bAr), 2.73 (1H, dd, J=13.4, 6.9 Hz, CH_aH_bAr), 2.50–2.35 (2H, m, CH_2CO), 2.43 (3H, s, NCH_3), 1.70–1.60 (1H, br s, NH); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 172.0, 138.5, 132.1, 129.3, 128.5, 126.4, 118.3, 65.1, 57.8, 40.1, 38.2, 33.7; HRMS (FAB): calcd for $[M+H]^+$ $C_{14}H_{20}NO_2$: 234.1494; found: 234.1491.

3.3.4. Allyl (*S*)-3-[*N*-butyl-*N*-*p*-nitrobenzenesulfonyl]-amino-4-phenylbutanoate (14). Anhydrous K_2CO_3 (300 mg, 2.2 mmol) was added in one portion to a solution of

crude **12** (300 mg, 0.74 mmol) and BuI (0.24 mL, 2.2 mmol) in dry DMF (5 mL) at room temperature. The resulting mixture was stirred at room temperature under N_2 for 19 h. Removal of the volatiles afforded a brown solid that was diluted with EtOAc (40 mL), washed with a 0.5 M aqueous solution of citric acid (2×40 mL) and brine (40 mL) and dried ($MgSO_4$). The solvent was removed to afford **14** (335 mg, 98%) as a brown oil that was used in the next step without further purification. An analytical sample was purified by flash chromatography (CH_2Cl_2) to afford pure **14** as a white solid; R_f=0.55 (CH_2Cl_2); mp 53–55°C; $[\alpha]_D$=−8.3 (c=1.0 in $CHCl_3$); IR (film): ν 3100, 3030, 2980, 2970, 1740, 1610, 1535, 1350, 1160; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.09 (2H, d, J=9.0 Hz, ArH), 7.73 (2H, d, J=9.0 Hz, ArH), 7.15–7.10 (3H, m, ArH), 7.05–7.00 (2H, m, ArH), 5.75 (1H, ddt, J=17.0, 10.5, 6.0 Hz, CH_2CH=CH_2), 5.20 (1H, dq, J=17.0, 1.5 Hz, CH_2CH=CH_aH_b), 5.16 (1H, dq, J=10.5, 1.5 Hz, CH_2CH=CH_aH_b), 4.40–4.30 (3H, m, NCH and CH_2CH=CH_2), 3.18 (2H, t, J=8.0 Hz, NCH_2), 2.87 (1H, dd, J=13.8, 7.2 Hz, CH_xH_y), 2.80 (1H, dd, J=13.8, 7.5 Hz, CH_xH_y), 2.67 (1H, dd, J=16.4, 7.0 Hz, CH_aH_b), 2.54 (1H, dd, J=16.4, 7.5 Hz, CH_aH_b), 1.62–1.48 (2H, m, NCH_2CH_2), 1.30–1.20 (2H, m, $NCH_2CH_2CH_2$), 0.87 (3H, t, J=7.5 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 170.3, 149.6, 146.5, 137.3, 131.6, 129.1, 128.6, 128.3, 126.9, 124.0, 118.8, 65.5, 58.0, 45.6, 40.2, 38.6, 32.8, 20.2, 13.7; HRMS (FAB): calcd for $[M+H]^+$ $C_{23}H_{29}N_2O_6S$: 461.1746; found: 461.1753.

3.3.5. Allyl (*S*)-3-butylamino-4-phenylbutanoate (16). Mercaptoacetic acid (112 μL, 1.6 mmol) and DBU (580 μL, 3.8 mmol) were added to a solution of crude **14** (230 mg, 0.5 mmol) in non-dried DMF (5 mL) under N_2 at room temperature. The resulting mixture was stirred for 17 h, concentrated under reduced pressure and diluted with EtOAc (30 mL), which was washed with a saturated solution of $NaHCO_3$ (2×30 mL), and brine (30 mL) and dried ($MgSO_4$). The solvent was removed to afford a brown oil that was purified by flash chromatography (hexanes/EtOAc 1:1) to give **16** (96 mg, 70%) as a yellow oil; R_f=0.45 (hexanes/EtOAc 1:1); $[\alpha]_D$=+6.4 (c=0.75 in $CHCl_3$); IR (film): ν 3040, 2980, 2970, 1740, 1150; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.35–7.15 (5H, m, ArH), 5.91 (1H, ddt, J=17.2, 10.4, 5.8 Hz, CH_2CH=CH_2), 5.31 (1H, dq, J=17.2, 1.5 Hz, CH_2CH=CH_aH_b), 5.23 (1H, dq, J=10.4, 1.4 Hz, CH_2CH=CH_aH_b), 4.65–4.50 (2H, m, CH_2CH=CH_2), 3.35–3.20 (1H, m, NCH), 2.83 (1H, dd, J=13.5, 6.5 Hz, CH_aH_b), 2.72 (1H, dd, J=13.5, 7.0 Hz, CH_aH_b), 2.65–2.55 (2H, m, CH_2), 2.45–2.40 (2H, m, CH_2), 1.50–1.20 (5H, m, CH_2CH_2 and NH), 0.87 (3H, t, J=7.5 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 172.0, 138.6, 132.1, 129.3, 128.4, 126.3, 118.3, 65.0, 56.3, 46.7, 40.6, 38.7, 32.2, 20.3, 13.9; HRMS (FAB): calcd for $[M+H]^+$ $C_{17}H_{26}NO_2$: 276.1964; found: 276.1977.

3.3.6. Allyl (*S*)-allylamino-4-phenylbutanoate (19). Anhydrous K_2CO_3 (3.74 g, 27.0 mmol) was added in one portion to a stirred solution of **4b** (4.09 g, 11.2 mmol) and allyl bromide (2.40 mL, 27.7 mmol) in non-dried DMF (40 mL) at room temperature. After 13 h mercaptoacetic acid (1.9 mL, 27.3 mmol) was added followed by DBU (16.5 mL, 110.4 mmol) and the mixture stirred for a further 2.5 h. The resulting suspension was diluted with EtOAc (100 mL), washed with a saturated aqueous solution of $NaHCO_3$ (3×50 mL), dried ($MgSO_4$) and the solvent removed to afford **19** (2.32 g, 80%) as an orange oil: R_f=0.38 (CH_2Cl_2/MeOH 10:1); $[\alpha]_D$=−1.1 (c=1.1 in $CHCl_3$); IR (film): ν 3180, 3030, 2900, 1725, 1440, 1135; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.31–7.26 (2H, m, ArH), 7.23–7.16 (3H, m, ArH), 5.90 (1H, ddt, J=17.5, 10.5, 5.5 Hz, OCH_2CH=CH_2), 5.82 (1H, ddt, J=17.0, 10.5, 6.0 Hz, NCH_2CH=CH_2), 5.31 (1H, ddd, J=17.5, 3.0, 1.5 Hz, OCH_2CH=CH_aH_b), 5.23 (1H, ddd, J=10.5, 3.0, 1.5 Hz, OCH_2CH=CH_aH_b), 5.14 (1H, ddd, J=17.0, 3.5, 1.5 Hz, NCH_2CH=CH_aH_b), 5.06 (1H, ddd, J=10.5, 3.0, 1.5 Hz, NCH_2CH=CH_aH_b), 4.58–4.55 (2H, m, OCH_2CH=CH_2), 3.32–3.26 (3H, m, NCH and NCH_2CH=CH_2), 2.85 (1H, dd, J=13.5, 6.5 Hz, CH_aH_bAr), 2.72 (1H, dd, J=13.5, 7.5 Hz, CH_aH_bAr), 2.42 (2H, d, J=6.5 Hz, CH_2CO), 2.10–1.90 (1H, br s, NH); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 171.8, 138.4, 136.6, 132.0, 129.3, 128.4, 126.3, 118.2, 115.8, 64.9, 55.3, 49.5, 40.4, 38.6; HRMS (FAB): calcd for $[M+H]^+$ $C_{16}H_{22}NO_2$: 260.1650; found: 260.1642.

3.3.7. Allyl (*S*)-3-[*N*-allyl-*N*-(9*H*-fluoren-9-yl)methoxycarbonyl)]amino-4-phenylbutanoate (20). (9*H*-Fluoren-9-yl)methyl chloroformate (2.30 g, 8.9 mmol) was added in small portions to a suspension of **19** (2.31 g, 8.9 mmol) and Na_2CO_3 (2.37 g, 22.4 mmol) in 2:1 H_2O/dioxan (30 mL) at 0°C and the resulting mixture was stirred at room temperature for 24 h. The mixture was diluted with EtOAc (150 mL), washed with a 0.5 M aqueous solution of citric acid (2×50 mL) and brine (50 mL), dried ($MgSO_4$) and the solvent removed to afford **20** (4.19 g, 98%) as a light orange oil: R_f=0.82 (hexanes/EtOAc 1:1); $[\alpha]_D$=−22.0 (c=1.0 in $CHCl_3$); IR (film): ν 3430, 3040, 2920, 1730, 1690, 1440, 1230; ^{1}H NMR ($CDCl_3$, 300 MHz; 1:1 rotamers ratio, asterisk denotes one of the rotamers) δ 7.82–7.72 (4H, m, ArH), 7.68–7.52 (4H, m, ArH), 7.12–7.44 (16H, m, ArH), 6.82–6.74 (2H, m, ArH), 5.87 (2H, ddt, J=17.2, 10.3, 5.7 Hz, OCH_2CH=CH_2 and OCH_2CH=CH_2^*), 5.52–5.34 (2H, m, NCH_2CH=CH_2 and NCH_2CH=CH_2^*), 5.32–5.27 (4H, m, OCH_2CH=CH_2 and OCH_2CH=CH_2^*), 5.26–4.96 (4H, m, NCH_2CH=CH_2 and NCH_2CH=CH_2^*), 4.76–4.86 (1H, m, $CHCH_aH_bO^*$), 4.74–4.64 (1H, m, $CHCH_aH_bO^*$), 4.58–4.38 (6H, m, $CHCH_2O$, OCH_2CH=CH_2 and OCH_2CH=CH_2^*), 4.28–4.21 (2H, m, $CHCH_2O$ and $CHCH_2O^*$), 4.18–4.10 (1H, m, CHN), 3.98 (1H, m, CHN^*), 3.64–3.54 (4H, m, NCH_2CH=CH_2 and NCH_2CH=CH_2^*), 3.15 (1H, dd, J=13.0, 8.5 Hz, CH_aH_bAr), 3.02–2.96 (2H, m, CH_aH_bAr and CH_aH_bCO), 2.68 (1H, dd, J=16.5, 6.0 Hz, CH_aH_bCO), 2.30–2.18 (2H, m, CH_2Ar^*), 2.16–2.04 (1H, m, CH_aH_bCO), 2.00–1.87 (1H, m, $CH_aH_bCO^*$); ^{13}C NMR ($CDCl_3$, 75.4 MHz; 1:1 rotamers ratio) δ 170.4, 170.1, 155.1, 154.4, 143.2, 140.6, 140.5, 137.4, 137.3, 133.4, 133.2, 131.2, 128.4, 128.3, 127.6, 127.4, 127.0–126.6, 126.3, 126.1, 125.6, 125.5, 124.1, 123.9, 123.6, 120.0–118.0, 117.4, 116.3, 116.0, 66.0, 65.6, 64.2, 56.9, 55.9, 49.8, 46.4, 38.1, 37.8, 36.5; HRMS (FAB): calcd for $[M+H]^+$ $C_{31}H_{32}NO_4$: 482.2331; found: 482.2331.

3.3.8. (*S*)-3-[*N*-Allyl-*N*-(9*H*-fluoren-9-yl)methoxycarbonyl)]amino-4-phenylbutanoic acid (17). To a solution of **20** (2.13 g, 4.4 mmol) in dry CH_2Cl_2 (40 mL) was added

$Pd(PPh_3)_4$ (95 mg, 84 μmol) quickly followed by Bu_3SnH (1.31 mL, 4.9 mmol) and the resulting mixture stirred under N_2 for 2.5 h. The solution was washed with 2 M HCl (2×20 mL) which was subsequently extracted with CH_2Cl_2 (10 mL). The organic portions were combined, dried ($MgSO_4$) and the solvent removed. The residue was dissolved in CH_3CN (100 mL), washed with hexanes (3×80 mL), the solvent removed and the resulting solid recrystallized from CH_3CN to afford **17** (1.05 g, 54%) as a pale yellow solid: R_f=0.47 (hexanes/EtOAc 1:1); mp 134–136°C; $[\alpha]_D$=−34.9 (c=1.1 in $CHCl_3$); IR (film): ν 3500–2300, 1690, 1435, 1230; ^{1}H NMR ($CDCl_3$, 500 MHz; 1:1 rotamers ratio, asterisk denotes one of the rotamers) δ 7.79–7.72 (4H, m, ArH), 7.62 (2H, t, J=7.5 Hz, ArH), 7.53 (2H, d, J=7.0 Hz, ArH), 7.41–7.10 (16H, m, ArH), 6.77–6.70 (2H, m, ArH), 5.50–5.35 (2H, m, CH_2CH=CH_2 and CH_2CH=CH_2*), 5.20–4.92 (4H, m, CH_2CH=CH_2 and CH_2CH=CH_2*), 4.88–4.74 (1H, m, CH_aH_bO*), 4.71–4.59 (1H, m, CH_aH_bO*), 4.50 (1H, dd, J=10.5, 7.0 Hz, CH_aH_bO), 4.40 (1H, dd, J=10.5, 6.5 Hz, CH_aH_bO), 4.21 (2H, m, $CHCH_2O$ and $CHCH_2O$*), 4.08–4.02 (1H, m, NCH), 3.95–3.65 (1H, m, NCH*), 3.64–3.48 (4H, m, CH_2CH=CH_2 and CH_2CH=CH_2*), 3.13–3.08 (1H, dd, J=13.0, 8.5 Hz, CH_aH_bAr), 2.95 (1H, dd, J=16.5, 8.0 Hz, CH_aH_bCO), 2.90 (1H, dd, J=13.0, 6.5 Hz, CH_aH_bAr), 2.68 (1H, dd, J=16.5, 5.5 Hz, CH_aH_bCO), 2.28–2.14 (2H, m, CH_2Ar*), 2.10–2.00 (1H, m, CH_aH_bCO*), 1.95–1.80 (1H, m, CH_aH_bCO*); ^{13}C NMR ($CDCl_3$, 75.4 MHz; 1:1 rotamers ratio) δ 176.8, 176.7, 156.1, 155.3, 144.0, 141.4, 138.1, 134.0, 131.8, 131.6, 131.1, 130.9, 130.3, 130.2, 129.9, 129.8, 129.6, 129.1, 129.0, 127.5, 127.0, 122.6, 122.5, 119.9, 119.7, 117.2, 117.1, 66.9, 66.5, 57.7, 56.5, 50.9, 47.3, 39.0, 38.6, 37.1; HRMS (FAB): calcd for $[M+H]^+$ $C_{28}H_{28}NO_4$: 442.2018; found: 442.2034.

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